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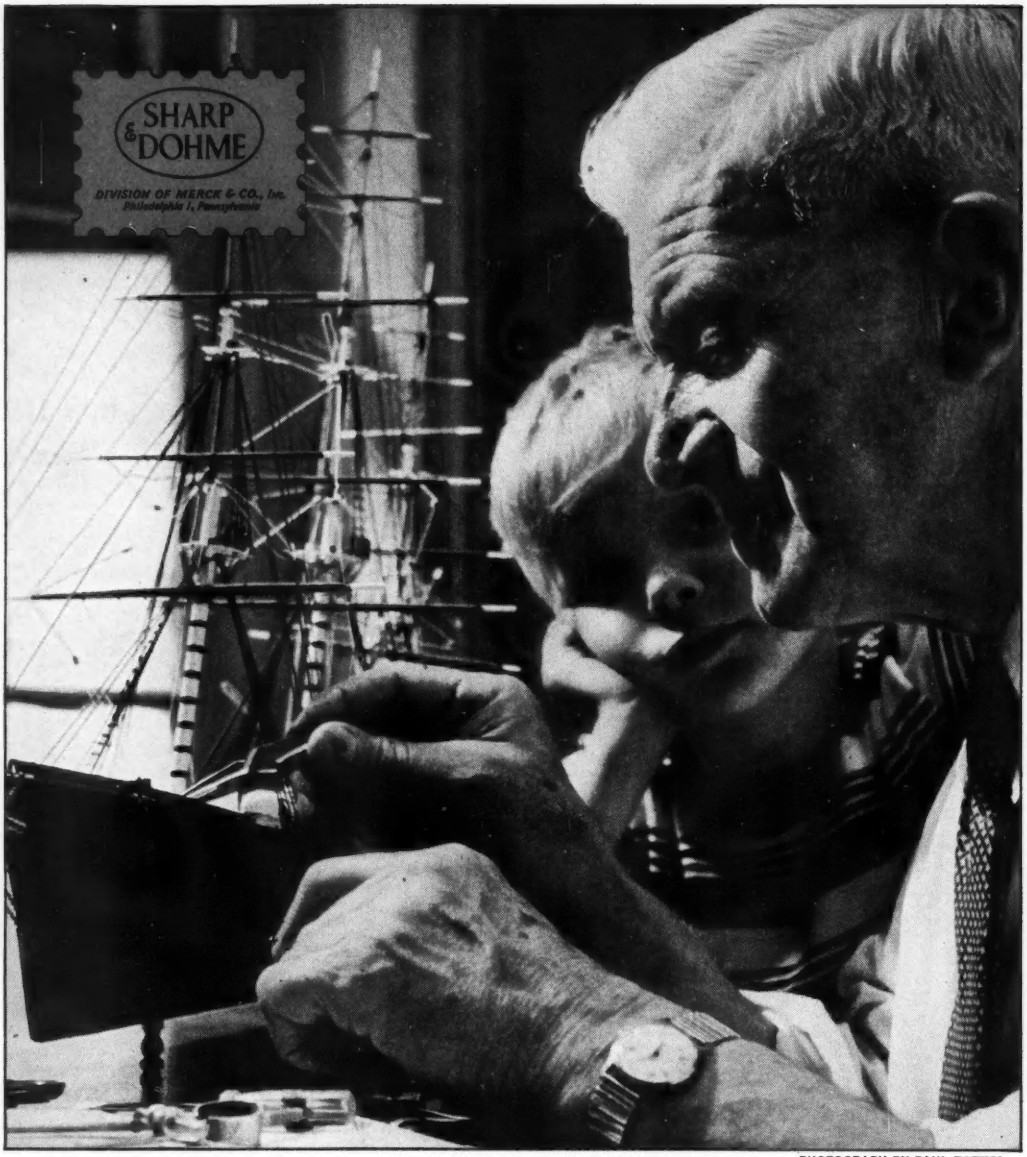

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California MEDICINE

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14,501 Deliveries With No Maternal Death

STIRLING PILLSBURY, M.D., Long Beach

• In 14,501 deliveries at one hospital there have been no maternal deaths. Several factors have contributed to this eight-year record:

1. Immediate availability of blood and liberal use in anemia and in abnormal bleeding has prevented deaths from hemorrhage.

2. Antibiotics and early ambulation have reduced infections.

3. Spinal anesthetics reduce hemorrhage and allow for greater flexibility in combating complications at delivery.

4. Consultations are required for certain complications, are freely available in all cases, and give the advantage of two opinions instead of one.

5. Good nursing care is essential.

MATERNAL MORTALITY throughout the United States has been reduced from 79.9[1] per 10,000 births in 1920, to 20[1] in 1945, and to the low figure of 7 in 1952. Physicians are striving, however, to reduce this percentage still further.

During the last eight years, from 1945 to 1953, 14,501 mothers have been delivered at Seaside Memorial Hospital in Long Beach without a single maternal death from obstetrical or any other cause. Seaside Memorial Hospital is a 370-bed general hospital, with a 40-bed obstetrical service. The patients were cared for by more than 118 physicians, 35 of whom were interns. The 14,501 deliveries include 731 cesarean sections, an incidence of 5 per cent.

The average maternal death rate throughout the United States for this same period was 12.9[1] per 10,000 births, or 18.7 deaths in 14,501 deliveries. Although the maternal mortality rate for any hospital should be lower than for the United States as a whole, nevertheless 14,501 births with no deaths indicates salvage of several mothers more than the average.

The hospital staff believe that several factors have contributed to this record:

Combating of hemorrhage, the principal cause of maternal death, by preventive measures and by replacement of lost blood. During the first three years included in this report blood was obtained from commercial sources in fair amount and was nearly always available when needed; during the last five years the American Red Cross has maintained an adequate supply. In 1952, 285 pints of blood were used in the obstetrical department, an average of 13 units per 100 deliveries. One patient alone received 19 pints.

Blood type and cross-matching tests are made immediately on all obstetrical patients admitted for cesarean section or with more than average bleeding, and in such cases blood is readied for immediate use. Physicians are urged to give transfusions to all severely anemic patients before or after delivery.

Use of antibiotics for infection, which is the second most important cause of maternal death. Antibiotics are given in large doses on significant rise in

Presented before the Section on Obstetrics and Gynecology at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24-28, 1953.

Statistics for this presentation were compiled by N. J. Thysell, M.D.

temperature without waiting to make a definite diagnosis. This practice may be unscientific, but it has had the desired effect.

Special treatment of toxemia, third among fatal conditions in childbirth. In all cases of toxemia the physician is required to consult with one of the obstetrical committee, and usually is requested to consult with the medical staff also. Pregnant patients with mild toxemia are assisted to carry their babies as near to term as possible in the hope of obtaining a viable child. In more severe toxemia glucose (usually in 5 per cent solution) is given intravenously and sedation is effected with one of the barbiturates, morphine and magnesium sulfate. If there is no improvement in toxemia the uterus is emptied by the safest method. Convulsions are usually controlled by the intravenous administration of barbiturates, and oxygen is given; the uterus is emptied by the safest route as soon as the patient's condition permits. As prenatal care improves toxemia occurs less frequently.

Postpartum toxemia is in many cases observed early by the nursing staff, who determine blood pressure frequently. The condition is controlled with sedation and dietary measures. The newer antihypertensive drugs have not been used, but these should be seriously considered.

Early ambulation, first practiced in 1946, has become increasingly accepted until at present few patients are confined to bed more than 12 hours after delivery. This measure, by stimulating the circulation, has reduced the incidence of infection, especially in the pelvis, lungs and legs. Thrombosis is extremely rare, and there has been no proven occurrence of embolism in the cases covered by this report.

Low spinal anesthesia or saddle block was begun in 1946 and has been used in an increasingly large proportion of cases (31 per cent in 1947, 48 per cent in 1950-52). In most cases spinal anesthetic is given by an anesthetist. It is required that a physician, other than the attending obstetrician or a member of the house staff, be in attendance after the anesthetic has been given. This rule at first caused some objection, mainly because of the added charge, but it has been rigidly applied and has become quite well accepted in the last few years. There is grave danger in leaving unattended a patient under any major anesthesia.

Spinal anesthesia, supplemented by the use of sodium pentothal or gas following delivery, has been used in 92 per cent of the cesarean sections included in this survey. No serious complication has resulted from spinal anesthesia in over 5,000 deliveries in which it was used, and no financial liability has been incurred.

Experience with spinal anesthesia indicates these advantages: The mother is completely relieved of pain. The baby is less in danger of anoxemia. Uterine contractions are not affected, and therefore there is less likelihood of hemorrhage. The birth canal is more relaxed so that the baby can more easily be delivered and complications that may arise can be more easily overcome. The possibility of inhalation pneumonia is eliminated. Regarding this last danger, Hingson[2] in 1951 reported 59 maternal deaths due to aspiration pneumonia following inhalation anesthesia and estimated that 2 per cent of all maternal deaths are due to this cause. Ether anesthesia administered by a nurse is still common at Seaside Memorial Hospital but is not regarded as a procedure of choice.

Consultation, required in certain circumstances and freely used regarding any abnormality, is of prime importance in the prevention of serious complications. In the cases here reviewed, almost 55 per cent of the patients were cared for by general practitioners or interns; all physicians, however, must obtain written permission from a member of the obstetrical consultation committee for high forceps delivery, cesarean section, induction of labor by mechanical means, or internal podalic version. This rule not only prevents physicians from attempting procedures for which they are not qualified but also assures another opinion as to the advisability of the procedure considered. It is to be noted that neither high forceps delivery nor internal podalic version has been done in the last five years. Induction of labor by mechanical means merely for the patient's or the physician's convenience is not permitted.

Consultation with a member of the committee is also required in all cases with excessive hemorrhage either before or after birth, reduction of hemoglobin to less than 50 per cent of normal, thrombosis, hypertension with systolic blood pressure over 160 mm. of mercury, convulsion, fever of 102.6° F. or higher lasting more than 24 hours, obstruction to delivery, or prolonged labor.

The obstetrical consultation committee consists of five members who are either diplomates of the American Board of Obstetrics or eligible for the diploma. No charge is made for obligatory consultations, and rarely is there a charge for assistance by one of the committee at delivery. Both specialists and general practitioners have recognized that the primary interest of the committee is in the welfare of the patient, and this recognition has resulted in a very friendly and cooperative atmosphere in the obstetrical department.

The nursing staff must be given full credit for their share in saving lives. They are constantly on the alert for abnormal signs and symptoms, checking blood pressure as each patient is brought to a labor

room, during labor, and after delivery, and observing bleeding, the height of the fundus and other indications.

117 East Eighth Street.

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1. U. S. Summary of Vital Statistics, Vol. 36, No. 22, Sept. 10, 1952.

2. Hingson, R.: Research in Anesthesia and Analgesia, 30:121, May-June 1951.

***Discussion by* DONALD A. DALLAS, M.D., San Francisco**

On hearing the original title of this presentation, "13,000 Deliveries Without a Maternal Death," I assumed that it meant 13,000 deliveries without an obstetrical death. When I found that it meant—at the latest figure—14,501 consecutive deliveries without a death from any cause, I must admit that I was skeptical.

To those of us who have been active in obstetrics for more than 25 years, this report seems almost incredible. Twenty years ago an analysis of 14,501 consecutive deliveries in a general hospital would almost inevitably have reported at least 45 maternal deaths.

I will present for comparison the maternal mortality statistics from the hospital in which I do most of my work. In The Hospital for Women and Children in San Francisco, 13,509 patients have been delivered in the last six years. Of these, approximately 11,000 were private patients and 2,500 were clinic patients. Most of the private patients were cared for by specialists, a small percentage by general practitioners. The clinic patients were delivered by the house staff under supervision. Consultation is not required but is frequently made use of. All anesthetists are physicians. Continuous caudal and low spinal anesthesia are widely used, general anesthesia less so. Blood is constantly available in the hospital. The nurses are well trained, conscientious, and adequate in number. The type of obstetrics practiced is largely operative; 75 per cent of the deliveries are by forceps, 10 per cent by cesarean section, 12 per cent are spontaneous, and 3 per cent are by breech extraction.

There were five maternal deaths in this series of 13,509 consecutive deliveries. Only one of the five was an obstetrical death. Surprisingly, three of the others were due to spontaneous subarachnoid hemorrhage and one to acute anterior poliomyelitis.

***Discussion by* DONALD G. TOLLEFSON, M.D., Los Angeles**

As the author points out, hemorrhage must be treated early and adequately as it is the chief cause of death. It would be interesting to know how many cases of placenta previa and of abruption of the placenta were treated by cesarean section in the series reported.

Treating the infection early with antibiotics and undoubtedly the use of them in the long labor with early rupture of the membranes have solved the third most serious cause of death in childbirth.

Great emphasis should be placed on the early interruption of pregnancy for toxemic patients who do not respond to treatment.

The use of low spinal or saddle block in 48 per cent in the last part of the series is very high, but no morbidity or complications resulted. Insurance underwriters take note. Emphasis on the need for a physician other than the obstetrician to watch the patient should be required in all obstetrical departments.

The only point which might be open to question is whether spinal anesthesia helps to avoid anoxia in the child.

Peripheral Arteriosclerosis

Present Concepts of Management

EDWIN J. WYLIE, M.D., and RICHARD E. GARDNER, M.D., San Francisco

• Three hundred patients with clinical manifestations of ischemia due to peripheral arteriosclerosis were studied. An accurate demonstration of the extent of the arterial occlusive process by means of aortography was of major importance in determining therapy and prognosis.

The results from thromboendarterectomy to restore the arterial lumen in cases of segmental thrombosis or stenosis greatly exceeded those obtained from other methods of therapy for peripheral arteriosclerosis. The indications for and the limitations of lumbar sympathectomy as a palliative procedure are described. Medical treatment, except for the use of specific protective measures, was of little value in altering either the symptoms or prognosis.

RECENT DEVELOPMENTS in the diagnosis and treatment of arteriosclerosis as it pertains to peripheral vascular disease have altered many of the former concepts concerning the management of patients with this disease.

The necessity for precise methods of diagnosis based on an accurate definition of pathological changes has been recognized as the principal requisite in the management of any disease. Many of the former studies on the therapy of peripheral arteriosclerosis were necessarily empiric in their approach, owing to the lack of such methods. The recent extensive use of arteriography to demonstrate the degree and location of alterations in the flow of blood has supplied valuable information to guide both the diagnosis and the treatment of the varied peripheral ischemic manifestations of arteriosclerosis. Coincident surgical advances, aided by the information supplied by arteriography, have shown that definitive operative procedures are possible to restore normal blood flow through occluded arteriosclerotic arteries.[1, 4] The longer cumulative experience with the recognized palliative types of therapy has also tended to integrate theoretical concepts with clinical results.

During the recent five-year period in which many of the former concepts of the management of peripheral vascular disease have undergone revision, 300 patients with peripheral arteriosclerotic vascular disease were studied at the University of California Hospital and the San Francisco Hospital. The current ideas governing the management of peripheral arteriosclerosis are presented on the basis of this experience.

Over the period of the study, arteriography became the most important adjunct for the appraisal of ischemic syndromes resulting from peripheral arteriosclerosis. Inasmuch as the clinical significance of arteriosclerotic obliterative disease primarily concerns the arteries supplying the lower extremities, an adequate technique for the demonstration of these vessels was necessary. A modification of the formerly described methods of translumbar aortography has been found to be the most satisfactory for this purpose (Figure 1). The objective was to demonstrate clearly the sites of arterial disease, the portion of the arterial tree involved by significant disease, and the nature of collateral pathways.* For adequate visualization it was found necessary to use a large volume of contrast solution (50 cc.) and to inject it rapidly. This is of particular importance if there are multiple levels of occlusive lesions. It is recognized also that accurate evaluation of the prognosis and operability requires a demonstration of the full length of the arterial tree from the level of the diaphragm to the lower legs (Figure 2).

Aortography has been used extensively for only the past two years, during which time 155 aortograms have been performed. In 68 of the patients thus studied, later surgical exploration permitted the confirmation of the x-ray findings. These observations, combined with observations on the clinical progression of the ischemic states, have made it possible to define separate categories of peripheral ar-

From the Division of Surgery and the Vascular Clinic, University of California School of Medicine.

Presented before the Section on General Surgery at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24 to 28, 1953.

*The technique currently employed is as follows: The patient is placed prone over a cassette tunnel in which slots are provided for two 14- by 17-inch Lysholm wafer grids and a 14- by 36-inch cassette. The x-ray tube is fitted with a rectangular cone and an aluminum filter tapered to permit equal penetration of the abdomen and the less dense extremities. Under general anesthesia, two 17-gauge, 7-inch needles are inserted, one inch apart, into the abdominal aorta proximal to the celiac axis. Fifty cc. of 70 per cent Diodrast, or 70 per cent Urokon, divided between two syringes, is injected manually over a 4-second interval through the two needles. Four 36-inch films are exposed serially over an 8-second interval. The x-ray factors for the average patient are 81 kv, 400 ma, and 1/5 second, at a distance of 6 feet.

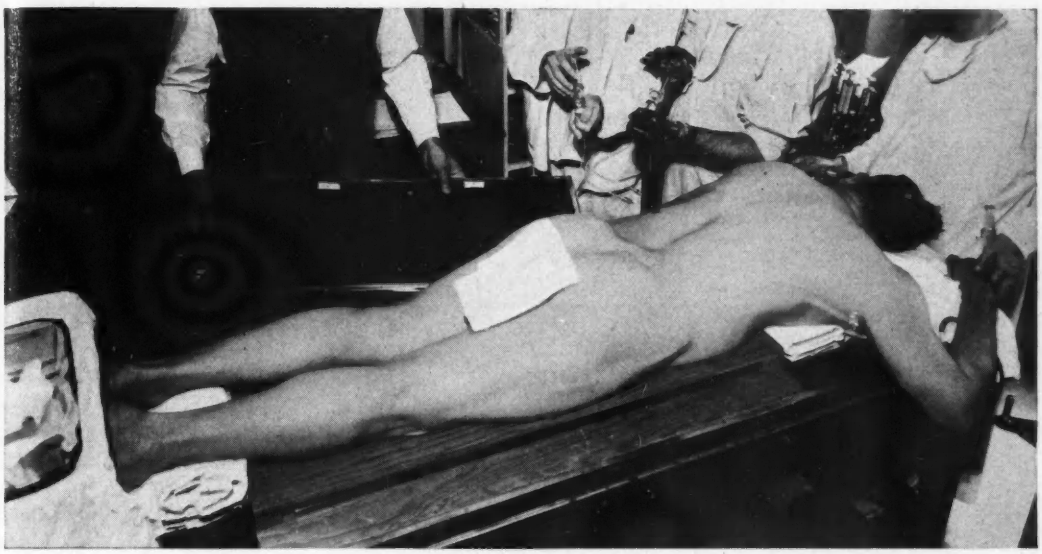

Figure 1.—Photograph illustrating the method of translumbar aortography used in the diagnosis of the extent and localization of arterial abnormalities between the level of the upper abdominal aorta and the popliteal arteries.

teriosclerosis and to correlate the signs and symptoms in each category with specific types and levels of arterial occlusions.

On the basis of the clinical and arteriographic studies, two categories of peripheral arteriosclerosis may be differentiated, depending upon the size of the artery involved and the extent of the occlusive process. These are: (1) segmental arterial thrombosis or stenosis; and (2) diffuse arterial thrombosis or stenosis. The therapy and prognosis vary in each category. In each, the basic lesion is complete or nearly complete arterial occlusion. Arteriosclerosis of the arterial wall, without obstruction to flow of blood, does not appear to be significant in the production of peripheral ischemia. In 96 per cent of the 300 patients, the principal impediment to flow of arterial blood was obstruction of arteries the size of the popliteal artery or larger. In most of these patients, there was relatively little obstructive involvement of the smaller arteries. Significant ischemia, solely as a result of occlusion of arteries distal to the popliteal artery, was observed in only 12 patients.

SEGMENTAL ARTERIOSCLEROSIS

The characteristics of localized segmental arteriosclerosis have only recently been studied and are of particular significance in view of the feasibility of direct surgical approaches to restore normal blood flow. Aortography has shown that approximately one-half of the patients with occlusion of arteries proximal to the popliteal artery have thrombotic occlusion that is limited to a segment of the major arterial tree. It must be acknowledged, however, that the fact that the authors have particular interest in this type of peripheral arteriosclerosis may have attracted a disproportionate number of patients in this category. The clinical and operative experiences previously reported with occlusions of this kind have suggested that the following is the mechanism in the segmental limitation of arterial occlusion:[2] The early arteriosclerotic lesion is a short zone of intimal thickening which, as it increases in depth, gradually encroaches upon the arterial lumen. This is most commonly observed near the orifice of a major arterial branch. Dilatation of the collateral vessels bypassing the stenotic zone is frequently observed in arteriograms taken at this stage. When complete occlusion develops in the stenotic segment, the static column of blood proximal and distal to the level of occlusion clots as far as the level of major arterial branches. Arteriograms taken at this time usually show filling of a major collateral artery at the proximal level of occlusion and a return flow of blood into the thrombosed artery at the lower level of occlusion by reverse flow through the distal collateral artery. Occlusions in the aorta, iliac, and common femoral arteries tend to remain localized to a short arterial segment because of the short distance between large arterial branches and the size of these branches. For the opposite reason, occlusions of the superficial femoral artery tend to be lengthy, extending from the profunda femoris to the popliteal artery. An additional observation has been that, with occlusion at the aortic and iliac levels, significant arteriosclerotic changes at lower levels are rare; with occlusion at

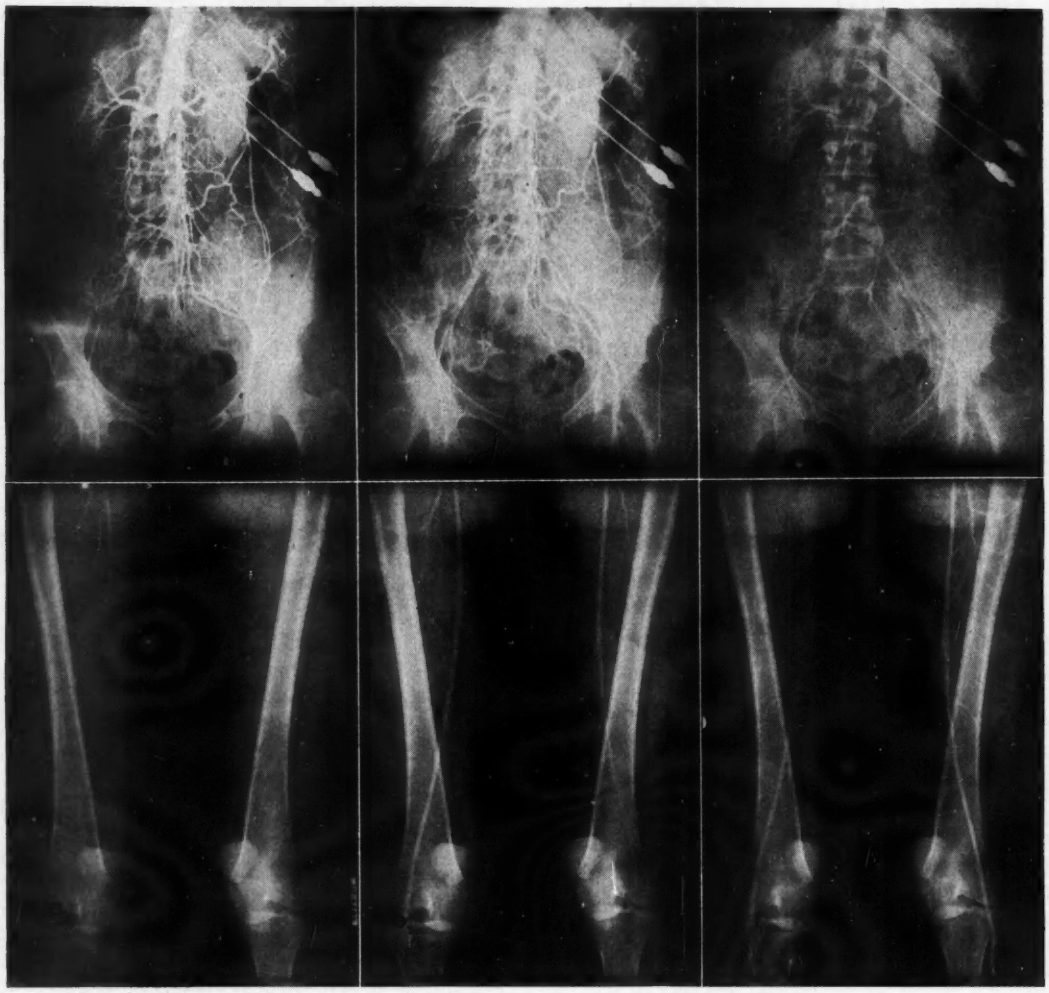

Figure 2.—Serial aortograms exposed at two-second intervals. The patient was a 43-year-old woman with segmental arteriosclerotic thrombosis of the terminal abdominal aorta and common iliac arteries. Note the collateral filling of the external iliac arteries by way of the hypogastric arteries (*B*), and the absence of significant luminal irregularities or narrowing in the distal arterial tree (*C*).

the femoral level, arteriosclerotic changes both proximal and distal to the occluded segment are frequent.

The average age at onset of ischemic symptoms in a series of 58 patients upon whom operation has been performed for segmental arteriosclerotic stenosis or thrombosis has been found to be considerably less than was formerly recognized in peripheral arteriosclerosis.

The tabulation of their ages by decades follows:

Ages	Number of Patients
30 to 39	7
40 to 49	22
50 to 59	21
60 to 69	7
70 to 79	1
Total patients	58

Twenty-nine of the patients (50 per cent) were under the age of 50. The level of the diseased arterial segment was above the external iliac artery in 43 patients. In this latter group considered alone, 25 (58 per cent) were under 50 years of age and 6 (14 per cent) under 40 years of age. The youngest patient was 30 years old.

A presumptive diagnosis of the level and extent of segmental arterial stenosis or thrombosis may usually be made from the history and physical findings. Occlusion of the superficial femoral or popliteal arteries is associated with claudication in the calf. Occlusion of the common femoral and external iliac arteries may also cause claudication in the calf but, due to the interference with flow of blood through

the profunda femoris, symptoms in the thigh musculature are produced. Symptoms at the thigh level are rarely those of pain. The more common complaint is muscular fatigability or weakness, produced by walking and relieved by rest, and usually localized to the posterior muscle groups of the thigh. Occlusion at the common iliac level produces, in addition to thigh fatigability, similar symptoms in the gluteal muscles. Pain in the low back and hip, after exercise, may also be complained of. These symptoms are believed to arise from decreased flow of blood through the hypogastric artery. In males, when the obstruction is bilateral, either from bilateral common iliac or aortic occlusion, impotence is almost universal. This is characterized by inability to attain or to maintain penile erection. In both sexes, hypesthesia in the perineal area following exercise is an occasional complaint. The diagnosis of arterial occlusive disease when it occurs at the level of the aorta or iliac arteries is often overlooked. This has been due to the relative youth of the patients and the dissimilarity of their complaints to those usually attributed to arteriosclerotic vascular disease.

Stenosis of a major artery, which is believed to be an intermediary stage in the development of arterial thrombosis, may also produce symptoms similar to those described above. Faintly palpable pulses may be detected in the arteries distal to a complete occlusion. This is most often observed with occlusions at the aortic or iliac level. In the presence of stenosis alone at this level, the peripheral pulses are stronger and are associated with an audible bruit over the femoral artery. Abnormal blanching of the foot on elevation of the leg is characteristic of lesions of both types.

Arterial stenosis sufficient to produce symptoms of ischemia has been found to indicate narrowing of the arterial lumen to less than 10 per cent of the normal size.[2] In six of 26 patients discovered to have segmental arteriosclerotic stenosis, the condition progressed to total occlusion over an observation period after the diagnosis was established by aortography. For these reasons, it is believed that the early recognition of arterial stenosis is of particular importance when symptoms of peripheral ischemia are apparent.

An accurate diagnosis in cases of segmental arteriosclerotic disease has special therapeutic significance. Thromboendarterectomy, an operation originally described by dos Santos of Lisbon, makes it possible to reestablish normal circulation in cases of segmental arteriosclerotic thrombosis or stenosis. This operation is based upon the observation that it is feasible to remove the diseased interior of an artery that is thrombosed due to arteriosclerosis and to use the preserved outer coat of undiseased media

Figure 3.—Aortogram of a 51-year-old man showing arteriosclerotic stenosis of the common iliac arteries. This patient complained of bilateral thigh and gluteal fatigability limiting his walking tolerance to one-half block, and of sexual impotence. All symptoms were relieved following endarterectomy.

to reconstruct a functioning artery. Experience with this operation on the University of California Surgical Service was initiated by animal experiments, and the operation was first successfully carried out in a human patient in January 1951.[3] Since that time, thromboendarterectomy has been performed on 58 patients. The operative technique was described in a previous report.[1] Results with respect to the restoration of arterial patency are shown in Table 1, and clinical results in Table 2.

Forty-two patients were significantly improved as a result of operation. In 35, the pedal pulsations were restored to normal volume and all symptoms and signs of ischemia relieved. Of 15 patients with

TABLE 1.—*Operative results of thromboendarterectomy—58 cases*

Level of Thrombosis	Number of Cases	Pedal Pulsations Restored After Operation	Distal Thrombosis Present Before Operation	Distal Thrombosis Appeared After Operation	Postoperative Thrombosis at Zone of Resection	Post-operative Deaths
COMPLETE OCCLUSION:						
Aorta and Iliac	15	11	1	1	1	2
Aorta, Iliac and Femoral	1	....	....	1	....	....
Iliac	8	7	1	....	....	2
Iliac and Femoral	3	1	1	....	1	1
Femoral	14	10	2	1	1	2
INCOMPLETE OCCLUSION:						
Aorta and Iliac	16	11	3	1	1	....
Femoral	1	....	....	....	1	....
TOTAL	58	40	8	4	5	7

TABLE 2.—*Clinical results of thromboendarterectomy*

	Pedal Pulsations Restored	Distal Thrombosis Present Before Operation	Distal Thrombosis Appeared After Operation	Post-operative Thrombosis at Zone of Resection
Improved	35	5	2	0
No change	....	0	0	5
Amputation	....	2	1	0
Died	5	1	1	0
Total	40	8	4	5

impotence due to aortic or iliac occlusion, 12 reported restoration of sexual potency. Five of the patients in the "improved" group had arterial occlusion distal to the operative area before operation. Decision for operation in such cases was based upon the possibility of improving the supply of blood to the extremity by relieving the more proximal obstruction. Thrombosis distal to the operative area developed during operation in two patients, but the continued patency of the larger proximal arterial segment caused definite improvement in supply of blood to the involved extremity. Thirty-two of the patients have been followed for over one year after operation and 11 for over two years. The immediate result has been sustained in all but two patients; they had segmental femoral thrombosis and arterial occlusion developed one year after operation. Both patients had been shown by x-ray to have diffuse arteriosclerotic changes before operation, as evidenced by multiple luminal irregularities in the patent major arteries. In four patients, areas of peripheral gangrene healed; and in four pain during periods of rest disappeared. Many of the patients in this group had been treated previously by medical measures or by lumbar sympathectomy. The circulatory improvement following thromboendarterectomy in patients with segmental arterial thrombosis greatly exceeded that obtained from any of the other methods of treatment.

In five patients, thrombosis developed at the zone of resection within the first hour after operation,

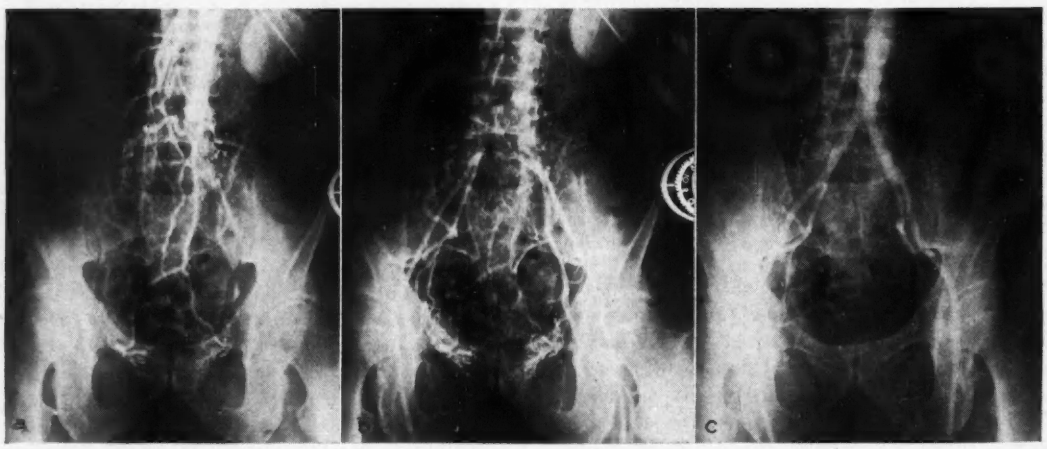

Figure 4.—Serial aortograms (*A* and *B*) of a patient with segmental thrombosis of the aorta and iliac arteries. Following thromboendarterectomy, pedal pulses were restored and all symptoms relieved. Aortography four months after operation (*C*) showed a normal arterial lumen.

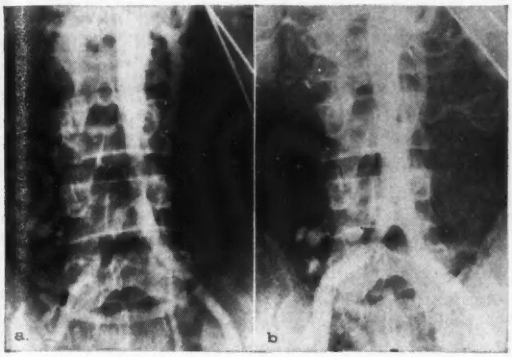

Figure 5.—Aortograms of a 46-year-old man with symptomatic stenosis of the terminal aorta before (*A*) and after (*B*) endarterectomy. (Figure 5 used by permission of *Surgery, Gynecology and Obstetrics.*)

Figure 6.—Bilateral serial femoral arteriograms obtained by injection of the abdominal aorta showing segmental thrombosis of the right superficial femoral artery. Note the multiple arteriosclerotic changes in the right popliteal artery distal to the occluded segment and, to a lesser degree, in the left femoral artery, indicating diffuse arteriosclerosis. Thromboendarterectomy was not advised for this patient.

resulting in a return to the preoperative status. Improved methods of anticoagulant therapy have minimized this hazard in later operations. Two of three patients upon whom amputation was later performed had distal gangrene prior to operation and had been shown to have multiple arterial occlusions in the lower legs. The third was the only patient in the series in whom thromboendarterectomy precipitated distal thrombosis leading to gangrene and amputation.

The operative mortality was 13.8 per cent. Death was due to cerebrovascular accidents occurring late in the postoperative period in two cases; to renal failure following a prolonged period of hypotension at operation in two; to mesenteric arterial occlusion in one; and to unknown cause in one. With improvement in the selection of patients and in operative technique, the mortality was reduced to less than 8 per cent in the second half of the series.

DIFFUSE ARTERIOSCLEROSIS

Diffuse arteriosclerosis is characterized arteriographically by multiple irregularities of the arterial lumen throughout the length of the arterial tree. In all cases studied in this category, there was one zone or more of complete occlusion or pronounced stenosis (Figure 6). The arterial tree proximal to the popliteal artery showed significant narrowing or thrombosis in most of the patients. Ischemia resulting solely from occlusions of arteries distal to the popliteal artery was observed in fewer than 4 per cent. In patients with thrombosis or stenosis proximal to the popliteal artery, it was frequently difficult to distinguish clinically between diffuse arteriosclerosis and the purely segmental type previously described. The presence of gangrene or pain at rest with severe ischemia usually denotes multiple arterial occlusions. Gangrene was present in only six and rest pain in five of the 58 patients with segmental disease. Palpable cord-like thickening of the femoral artery in the presence of thrombosis of the aorta or iliac arteries is also suggestive of diffuse arteriosclerotic changes at lower levels. In most patients with arterial occlusion proximal to the level of the popliteal artery, arteriography was necessary to distinguish the category of the arteriosclerotic process.

Therapy for patients with peripheral ischemia secondary to diffuse arteriosclerosis is limited to palliative measures. Special care is necessary in the protection of the feet. Care is taken to avoid trauma, exposure to extremes of cold or heat, and infection, any of which may be the precipitating factor in the development of tissue necrosis. Patients with claudication are advised not to walk far enough to cause pain. Frequently relief from rest pain may be obtained by requiring the patient to sleep with the head of the bed 12 inches higher than the foot. Systemic vasodilatation by any of the drugs currently widely used for the purpose is only rarely attended by evidence of increased flow of blood to the extremity. Symptomatic improvement from the use of alcohol appears to be due only to dulling of the sensorium to the discomfort or pain of ischemia. The employment of Buerger's exercises, aside from giving the patient something to occupy his mind, has similarly been unrewarding. There has been no real evidence that prohibiting the use of nicotine has materially altered the evidences of ischemia or the progression of the disease. The use of contrast baths is usually more harmful than beneficial.

Benefit has been reported by many investigators from the regional vasodilatation produced by lumbar sympathectomy. Sympathectomy was performed on 125 patients in this series during the past five years.

Detailed studies to evaluate the changes in peripheral circulation were made on 50. These included oscillometry, measurements of walking tolerance, estimations of the sympathetic tone as determined by the skin temperature response to reflex vasodilatation, and recording of basal skin temperatures of the extremities when exposed in a room where the temperature is constant. The symptomatic and temperature response to lumbar sympathetic block was recorded. All studies were repeated after sympathectomy. Review of the data obtained showed that the indications for sympathectomy were more valid when based upon clinical observations than upon the more complicated laboratory studies. The collateral flow to the extremity tended to be improved in almost all cases, regardless of the level of the occlusion, the degree of vasoconstriction or the response to sympathetic block. The degree of improvement was greater in those extremities in which vasoconstriction, as evidenced by cyanosis and sweating, was superimposed upon organic occlusion.

Although the available evidence indicated that improved collateral flow of blood resulted from sympathectomy, the flow needed for relief of the manifestations of ischemia varied with the type of complaint and the degree of ischemia. Sympathectomy was of the greatest value for patients whose major complaint was claudication. The average patient with this complaint was found to have doubled his walking tolerance after operation. In many cases this was adequate to restore the patient to productive activity. The increase in peripheral skin temperature observed after sympathectomy suggests, moreover, that the improved arterial supply to the skin may in many instances prevent or delay gangrene. Sympathectomy was of less value in the more advanced ischemic states in which rest pain or necrosis had developed. The postoperative increase in supply of blood was adequate to relieve rest pain in nine of 14 patients with this complaint. In no case was the degree of restoration of function sufficient to permit more than limited activity. A useful index in judging the possible benefit to be gained from sympathectomy to relieve rest pain is the measure of the capillary filling pressure. Cutaneous blanching of the toes or forefoot, with the patient supine and the foot at the level of the heart, indicated gross inadequacy of the collateral supply. Operation was ineffective in producing sufficient increase in flow of blood to relieve pain in cases in which there was this degree of arterial obstruction. Local amputation after sympathectomy was successful in three of 12 cases in which there was gangrene of one or more toes. Little credit was given to the effect of sympathectomy, however, inasmuch as results were comparable in a control series of local amputations. As a result of this study, sympathectomy in peripheral arteriosclerosis has been recommended in those patients with ischemic symptoms (1) who have been demonstrated clinically or by arteriography to have the diffuse form of arterial disease; (2) who show only moderate decrease in capillary filling pressure; and (3) who have developed minimal or no tissue necrosis.

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Pediatric Endocrinology

Notes on Some Recent Advances

FRANK L. PLACHTE, M.D., Ph.D., Beverly Hills

• *Until recently, congenital adrenocortical hyperplasia has defied most medical and surgical therapeutic efforts. However, in properly selected patients, cortisone will suppress the abnormal cortical hormone production. This, in turn, will lead to previously inhibited maturation and developmental progress.*

Adrenocortical insufficiency calls for much diagnostic alertness, as early recognition and immediate treatment are of paramount importance. The available therapeutic means are beneficial, although their limitations and potential dangers should be heeded.

Among newly developed diagnostic techniques, thyrograms promise to be helpful in the study of thyroid hyperplasia and neoplasia. Thyroid cancer, occurring infrequently in childhood, should at the earliest possible time be treated surgically and with postoperative radiation therapy.

THE REMARKABLE PROGRESS of endocrine investigation with its impact on clinical medicine has opened new vistas and illuminated new problems. A few of the recent advances, of importance in both diagnosis and therapy, should be of especial interest to clinicians who deal with infants, children and adolescents.

CONGENITAL ADRENAL HYPERPLASIA

The studies of Wilkins and co-workers[2, 26-32] focused a great deal of attention upon congenital adrenal hyperplasia, an entity of clinical, embryological, developmental, social, psychological and pathological import. The more than occasional familial incidence of the condition is well known.[13] In females the clinical manifestations are pseudohermaphrodism and virilism; in males, macrogenitosomia praecox. The accelerated growth, muscular development and epiphyseal ossification, the early growth of puberal hair, and the progressive virilization are due to excessive secretion of adrenocortical androgens.

This abnormal production of androgens may be the only pathophysiological aberration. However, not infrequently it is associated with disturbed electrolyte regulation typical of Addison's disease, a complication leading to early death unless immediately and properly treated. An occasional patient with congenital adrenal hyperplasia will have hypertension. Very rarely the condition may be associated with signs of deficient regulation of carbohydrate metabolism.[25, 29]

Surgical and hormonal therapy (except with cortisone) of congenital adrenal hyperplasia has been disappointing. However, cortisone in proper dosage and administered at an optimal time will at least diminish the manifestations of androgenic overproduction (acne, hirsutism). In older girls it will permit the inhibited normal maturation processes to take their physiological course, as evidenced by breast development, vaginal estrinization, menarche and menstruation and adolescent feminine features and configuration. Somatic growth and development proceed equally well in boys, and in the older ones testicular maturation takes place. Early treatment with cortisone will prevent epiphyseal closure and stunting. The psychological and social benefits derived from the treatment are of importance in the adjustment of these patients to their surroundings. During cortisone administration a significant decrease in the urinary content of 17-ketosteroids and estroids takes place.

The congenitally hyperplastic cortices in all probability secrete abnormally large amounts of both androgens and estrogens. The latter have no discernible effect on females, as they are blocked by the even larger amounts of androgen. Both cortical androgens and estrogens will inhibit the secretion of pituitary gonadotropins, an interference which explains the gonadal immaturity.

The mechanism of action of the exogenous cortisone is thought to be an inhibition of pituitary production of adrenocorticotropin, causing a decrease of adrenocortical activity and permitting the release

Part of the Panel on What's New in Pediatrics presented before the Section on Pediatrics at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24-28, 1953.

From the Department of Pediatrics, University of Southern California School of Medicine, and the Endocrine Clinic of the Children's Hospital, Los Angeles.

of pituitary gonadotropins which, at the proper time, lead to gonadal maturation and unopposed normal secondary sex development.[28] The anomalies that were present at the start are, of course, not influenced by cortisone therapy.[12]

For the initial treatment (leading to maximal suppression of 17-ketosteroid excretion in about 5 to 10 days), Wilkins prefers intramuscular administration as the results are more predictable. Infants receive 25 mg. a day, whereas children eight years of age and older are given 50 mg. a day. The daily maintenance dose (which should be determined for each patient individually) is about 5 mg. for infants and about 25 mg. for older children. The spacing of intramuscular administration of cortisone (for example, 25 mg. every 4 days in the younger and 100 mg. every 4 days in the older group) appears to lead to therapeutic results as good as those obtained with daily administration. Due to the more transient effect of cortisone given orally, more hormone is needed when it is administered by mouth. The recommended dose for infants is 5 to 12.5 mg. a day, and for older children 50 to 75 mg. a day. It is given in two or three divided doses.

With therapeutic doses of cortisone it is apparently not possible to depress the 17-ketosteroid excretion beyond a certain level. The residual amounts of urinary steroids may possibly represent metabolic end-products of the exogenous cortisone. Attempt should be made to reduce the urinary ketosteroid level below 8 mg. a day. In order to avoid toxic effects of cortisone, it is desirable to use the smallest dose that will maintain the suppression of the abnormal adrenocortical activity. The determination of this maintenance dose should be guided in the individual patient by clinical observations as well as repeated determinations of urinary 17-ketosteroid content.

It is of considerable interest that cessation of long-continued cortisone treatment is followed by an increase of urinary ketosteroids, not, however, to the pretreatment level. This may mean that the cortisone-induced suppression of adrenocortical activity persists to some extent after administration of cortisone is stopped. Whether a still longer period of treatment might result in a greater or even permanent inhibition of the cortical overactivity is not known as yet. At any rate, it appears that an infant or child with congenital adrenal hyperplasia is in need of cortisone therapy for a long period to obtain the desired benefits.

In the few reported cases of patients with hypertension coexistent with congenital adrenal hyperplasia who were treated with cortisone, good response was noted: The blood pressure remained normal for as long as a two-year period of therapy.[19, 20, 29]

ADRENOCORTICAL INSUFFICIENCY

The recognition and immediate treatment of hypoadrenocorticism, a not very common disorder in the pediatric age range, are of paramount importance.[4, 8, 11, 17]

Particularly in the very young, the manifestations of cortical insufficiency are easily mistaken for those of other disorders, among them pyloric stenosis, enteritis and cardiac disease.[14] The clinical signs include: vomiting, which may be projectile; visible peristaltic patterning in some infants; dehydration; diarrhea; acidosis; anorexia; loss of weight or poor gain in weight; microcardia; increasing weakness; circulatory collapse. The content of sodium, chloride and carbon dioxide in the serum is less than normal; of potassium and nonprotein nitrogen, more than normal. The eosinophil response is abnormal. Eosinophilia may be manifest in peripheral blood. The hypoglycemia and pigmentation that are characteristic of Addison's disease in older children and adults may be absent in the disease during early life.

Rarely occurring in "pure" form, the disease is more commonly associated with congenital adrenal hyperplasia. Signs of the latter or the appearance of abnormal sex manifestations in early life should warn of the possibility of incipient adrenocortical failure. Whether or not associated with another disorder, cortical insufficiency necessitates immediate action. In undiagnosed cases a clue to the underlying disorder may be given by the dramatic response to saline administration. In a number of cases the patients are known to have averted cortical failure, at least temporarily, by eating salt.

The therapeutic armamentarium for patients with cortical insufficiency includes cortical extracts, sodium chloride, cortisone and DOCA (desoxycorticosterone acetate).[2, 22] In "mixed adrenal disease," the administration of cortisone for the suppression of cortical overactivity should be undertaken with the consideration that cortisone is known to alter the requirements for DOCA. As to DOCA, it may, after a period of initial regulation, be administered in the form of pellets. Stress of one kind or another, including intercurrent infections, may necessitate a readjustment of therapeutic agents. The significant metabolic and toxic effects of excessive amounts of DOCA and cortisone should be constantly watched for and their appearance should lead to immediate reevaluation of therapeutic regimen.

In the fervor with which these and other endocrine agents are currently used, their obvious limitations must not be overlooked nor respect for their powerful metabolic and potentially harmful effects be lessened. In this connection, it is of considerable interest that cortisone injected into pregnant mice

produced cleft palate and other congenital malformations in the young. The earlier during gestation the cortisone was administered, the more severe were the defects observed in the young.[6]

DIAGNOSTIC PROCEDURES

To the array of well-established chemical, biological, histological, hematological and physical tests available for endocrine and metabolic studies (such as electrolyte and mineral determinations, hormone excretion studies and assays, tolerance tests, eosinophil response test, and radioactive iodine uptake studies) new and promising techniques have been added.

The cortisone-induced depression of urinary ketosteroids and estrogens in patients with adrenal hyperplasia helps in the differentiation between this condition and adrenocortical neoplasms. In the presence of the latter, cortisone does not suppress the urinary steroids.[15, 24, 27] By spectrometric test[7] it is possible to distinguish between androsterone and dehydroisoandrosterone. The latter steroid is often excreted in significant amounts by patients with cortical tumors.

The determination of adrenocortical response to exogenous corticotropin is a specific hormonal test and, particularly when the hormone is intravenously administered, has proven to be reliable. It serves in the differentiation of primary and secondary adrenocortical insufficiency.[23]

Testicular biopsies may be helpful in distinguishing between true sexual precocity and adrenal "precocity."[21]

The pronounced effect of injected thyrotropic hormone on the I^{131} uptake of patients with pituitary deficiency (secondary hypothyroidism) is a means of differentiating that condition from primary hypothyroidism.[16]

Functioning thyroid tissue containing adequate amounts of I^{131} can be visualized by scanning the gland with a directional scintillation counter. The resulting "scintigram" or "thyrogram" appears to be very helpful in the detection and study of hyperplastic and neoplastic disorders of the thyroid gland and in the search for aberrant thyroid tissue.[1]

CANCER OF THE THYROID GLAND

Thyroid cancer in children is rare.[9] Duffy and Fitzgerald,[5] reporting upon 28 cases in patients between 4 and 18 years of age, noted that these cases constituted 6.5 per cent of all cases of thyroid cancer observed at Memorial Hospital in New York. Horn and Ravdin,[10] in a study comprising 22 patients 25 years of age or younger, reported that those cases made up 13.8 per cent of all cases of thyroid cancer at the Hospital of the University of Pennsylvania.

The disease ordinarily runs a somewhat more benign and protracted course in persons in the younger age groups. Frequently there are long intervals between the onset of the disease (which relatively often occurs at the time of puberty) and definite diagnosis. The incidence of metastasis to cervical lymph nodes is high. The metastatic lesions may be present for years before the primary thyroid tumor is diagnosed.

It is generally agreed that the presence of a nodular goiter or any suspicious mass in the thyroid region should be considered a potentially malignant neoplasm until proven otherwise by excision and biopsy. Dailey and Lindsay[3] said that the likelihood of malignant disease is greatest if a nodule is solitary, if there has been recent enlargement, or if there is associated vocal cord paralysis.

The series from Memorial Hospital included nine patients who in the past had received radiation treatment to the thymus. However, Duffy and Fitzgerald did not feel that they could draw valid etiological conclusions. Horn and Ravdin mentioned that none of the 22 patients in their series had a history of previous radiation therapy for thymic enlargement.

Surgical extirpation and postoperative radiation treatment should be carried out at the earliest possible time. The use of radioactive iodine has definite limitations in this condition and should be reserved for a few selected patients. Rawson, Rall and Peacock[18] expressed belief that "treatment with radioactive iodine for cancer of the thyroid which is localized to the thyroid and adjacent lymph nodes and which can be removed by competent surgeons is indefensible."

8820 Wilshire Boulevard.

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No Conclusions by FDA on Boric Acid

THE FOOD AND DRUG ADMINISTRATION is investigating the use of boric acid in infants' preparations, but has come to no conclusions, according to Associate Commissioner John L. Harvey. He said there was no plan to restrict distribution. Mr. Harvey said FDA was reappraising the subject of boric acid toxicity, and when all the facts are in, "hopes to be in a position to determine whether there is any necessity for label changes or other steps in order to adequately protect the public interest." He said information was being obtained from pediatricians and other medical practitioners, as well as from sources from which "special studies of a controlled and reliable character" may be obtained.

—A.M.A. Washington Letter

What's New in Cerebral Palsy

MARGARET H. JONES, M.D., Glendale

• *Among new researches bearing on cerebral palsy are the growth of brain cells in tissue cultures for experimentation; the use of polysaccharides to prevent the formation of a glial barrier to nerve growth after injury; observation of changes in reactions of neurons at various stages of development; the finding of hypernatremia and hyperchloremia in lesions of the frontal lobe and the thalamus; stimulation of cerebral blood flow by injection of sodium bicarbonate and retardation with ammonium chloride; and studies of serial sections of brains of palsied children who died.*

Study of development in the early months of life has made possible the detection of significant abnormalities in behavior early in life. Loss of hearing may be tested in very young children by measuring minute variations in electrical resistance of the skin upon auditory stimulation of the sympathetic nervous system.

Conditions which have been described as having been confused with cerebral palsy are dislocation of a cervical vertebra, hereditary spastic paraplegia, transverse myelopathy, injury to the spinal cord or cauda equina by anomalous growths of the spine, and also encephalitis and meningitis.

Sedation has proved a valuable adjunct to electroencephalographic study of cerebral palsy. Better criteria for abnormality in the young child should be determined and the application of them more clearly standardized.

Simple exercises are useful for early training of palsied children to stimulate development. "Crossed laterality"—the dominant eye being contralateral to the preferred hand—has been counteracted by special training with great success in eliminating emotional and behavior problems and accelerating development.

Recent studies indicate that only 50 per cent of cerebral palsy patients have normal or better intelligence.

Subluxation of the hip joint, a common deformity associated with cerebral palsy, can sometimes be corrected by operation if detected at an early stage. Radical ablation of epileptogenic foci in the cortex is also being done in young patients if drug control of seizures fails. Frontal topectomy, cingulate gyrectomy or prefrontal lobotomy may be advisable in cases in which proper response to drug therapy is not obtained.

Improvement in behavior as well as control of seizures may follow the use of Benzedrine,® Dexedrine,® Dilantin® sodium, Mebaral® and phenobarbital. Alcohol, paraldehyde and chloral hydrate have been effective as relaxants.

IN REVIEWING BRIEFLY some of the recent work related to cerebral palsy, the author wishes to recommend Sir William Osler's five lectures on "The Cerebral Palsies in Children."[22] Little reference is made today to these excellent articles revealing an understanding of the problem which has not changed too greatly in the succeeding 65 years.

While progress continues in the treatment of cerebral palsy by physical therapy, drugs and surgical procedures, basic research in the pathological factors in this condition offers the best hope for early diagnosis and more effective treatment.

Part of the panel on What's New in Pediatrics presented before the Section on Pediatrics at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24-28, 1953.

1. *Basic Research Bearing on Cerebral Palsy*

Pomerat[26] has grown brain cells of various types in tissue cultures as a means of studying the direct effects of many factors in brain cells.

Crude liver or vitamin B_{12} has been found to affect the glial reaction so as to improve the status spongiosus as seen in the lateral columns in Addison's disease.

Permanent damage to the brain due to trauma at birth or afterward may be preventable by medication if the research of Windle, Clemente and Chambers[33] can be successfully pursued. They have been able with the use of a complex polysaccharide, Piromen,® to prevent the formation of a glial bar-

rier to the growth of peripheral nerves in the brain.

Development of brain metabolism studies by Hicks[14] indicates that neurons have widely different reactions at successive stages in development. For example, the neurectoderm is invulnerable to a wide variety of metabolic interruptions. The neuroblast is resistant to anoxia and hypoglycemia but sensitive to sulfhydryl and radiation and the "antisulfyl" action of steroids. Factors that affect glucose metabolism damage the neuron in a newborn child regardless of the oxygen level but, in the adult neuron, the damage is chiefly anaerobic. Interruption of normal steroid metabolism leads to neuron necrosis in the newborn but to marked interstitial and vascular changes in the adult.

In lesions of the frontal lobes and of the hypothalamus, according to Cooper,[8] hypernatremia (with 139 to 155 mg. of sodium per liter in the serum) and hyperchloremia (with 112 to 125 mg. of chlorides per liter in the plasma) usually occur, while the potassium content remains approximately normal. The mechanism causing this imbalance is not understood but may be the cause of some postoperative deaths.

Metabolic alkalosis which causes an increase of 65 per cent in the cerebral blood flow above the resting level may be produced by the intravenous injection of 3 per cent sodium bicarbonate, according to Schieve and Wilson,[29] who also found that a 0.8 per cent solution of ammonium chloride reduced the cerebral blood flow about 25 per cent.

Courville[9] has analyzed residual lesions resulting from antenatal and neonatal asphyxia in an attempt to link them with the abnormalities found in cerebral palsy. Other investigators have questioned whether factors other than anoxia may also be present in birth trauma. Magoun[17] and also Josephy are making studies of serial sections of the brains of children that died with cerebral palsy which it is hoped will lead to better understanding of this condition.

2. *Early Diagnosis*

Gesell and Amatruda[11] have outlined basic patterns of motor, language and personal-social development and by study of infants in the early months of life have been able to detect minor but clinically significant deviations from the norm which became more definite with age. Collis[7] concluded from clinical tests of mental activity in infants that "physical activity of the newborn infant does not display the influence of thought processes, but is entirely reflex . . . the reflex quality normally diminishes as competence emerges, and in the fourth month of life the change can be demonstrated. . . . in full term infants, at the fourth month of life deficient mental maturation is shown by lack of normal subordination of reflex processes; motor dysfunction, on the other hand, is shown . . . by failure of the reflex processes to operate normally in voluntary activity."

Although loss of hearing and loss of vision are frequent in cerebral palsy the early diagnosis of these defects is not easy. Hardy and Pauls[13] have described a "psychogalvanic skin resistance audiometer" developed at the hearing and speech center of Johns Hopkins Hospital. Without previous sedation the subject is seated comfortably and is amused while zinc electrodes are placed on the instep of each foot. Auditory stimulation of the sympathetic nervous system causes sufficient perspiration to reduce the resistance of the skin to the passage of a minute electrical current between the electrodes, from which the changes in voltage are transmitted and recorded.

3. *Differential Diagnosis*

Alexander, Masland and Harris[2] have described a case of anterior dislocation of the first cervical vertebra in which the symptoms of pallor and listlessness occurring at irregular intervals were attributed successively to congestion of the lung, to hypoglycemia, and to birth injury, as also to cerebral palsy.

Spastic paraplegia is another condition difficult to differentiate from cerebral palsy. Ford[10] described hereditary spastic paraplegia as a heredofamilial degenerative disease.

Recently described is transverse myelopathy[23] which resembles thrombosis of the anterior spinal artery but sometimes follows acute infectious diseases, the symptoms including ipsilateral weakness and contralateral loss of pain sensitivity and temperature control without loss of the senses of touch, vibration and position.

Also to be distinguished from cerebral palsy is diastematomyelia caused by the transfixion of the spinal cord or cauda equina by a bony spicule arising from the posterior aspect of a vertebra. In all the cases of this condition reported by Ingraham[16] there was also other anomaly of the spinal column. Neurologic impairment of the lower extremities and of the rectal and vesical sphincters was progressive, and in a number of cases there was a cutaneous midline defect.

The possibility of mistaking encephalitis and meningitis for cerebral palsy is illustrated by the case reported by Benda[4] of a child in whom the only early symptoms were retarded development in sitting, walking and talking, slight strabismus, and "walking with a wide base." Spasticity developed gradually from the age of six years and the child died at 11½ years. "Autopsy showed ample evidence of chronic productive encephalitis which was still in

a progressive state and which involved the cortical gray matter as well as the white matter and basal ganglia. Comparison with lesions in the case of rheumatic encephalitis indicated this diagnosis."

4. *Electroencephalographic Findings*

Of 1,287 children with cerebral palsy in Los Angeles County, 319 were examined by electroencephalogram.[32] Abnormalities were thus indicated in 66 per cent. Of the spastic children, abnormalities were indicated in 70 per cent, 43 per cent of the abnormalities being focal lesions. Abnormalities were likewise indicated in 50 per cent of the children with athetosis, 50 per cent being focal lesions. The percentage of abnormality indicated in "mixed types" was 71, and in children with ataxia, 66.

Ross, Grizzelle and Norfleet[28] studied the electroencephalographic records of 14 children to find whether certain facts of clinical importance could be determined from the records. They concluded that while the electroencephalogram indicates the extent and localization of cerebral lesions this information was not of clinically diagnostic value; intelligence potentials could not be determined from the readings, and prognosis regarding seizures was rarely possible.

In the review by Perlstein, Gibbs and Gibbs[25] of 212 cases of spastic and athetoid cerebral palsy in children, abnormalities were found in the electroencephalograms of 59 per cent of the spastic children who had not had seizures and in 95 per cent of those who had them. In 84 per cent of the spastic children the abnormalities were severe. Abnormalities were indicated in the recordings on 27 per cent of children with athetosis who had not had seizures and in only 67 per cent of those who had. In a series of unselected epileptic children 90 per cent had abnormalities evident in the electroencephalogram, while in normal controls abnormalities were indicated in only 16 per cent. In the recordings of children with cerebral palsy there was a greater frequency of spikes than in the recordings on children with epilepsy, while patterns characteristic of petit-mal and psychomotor disturbances were comparatively rare. They felt that certain inferences could be drawn from such data: "If there has been no history of seizures, the finding of a very abnormal electroencephalogram warns that clinically evident seizures may occur. If there has been no history of seizures the finding of a normal electroencephalogram gives some assurance that clinically evident seizures will not occur."

Aird and Cohen[1] in 1950 reviewed records of 187 cerebral palsy patients between 1 and 21 years of age and studied the electroencephalographic tracings in relation to type and degree of neuromuscular handicap. They concluded that "electroencephalography possesses the same diagnostic and prognostic value in this condition that it does in other neurological disorders associated in a high percentage of cases with cerebral pathologic change and dysfunction. Claims which either belittle its value in this condition or on the other hand stress its unique diagnostic potentialities in cerebral palsy, would appear unwarranted."

Gibbs,[12] at a round table on electroencephalography at the American Academy of Pediatrics meeting in October 1952, described a pattern characteristic of total disorganization (mountainous waves) associated clinically with mass stiffness and spasms. Children in whom these signs were observed almost always died by the age of three years. He stated that if the recording of the brain waves included the period just between sleeping and waking the number of abnormalities found was doubled in cases of epilepsy and increased by a third in cases of psychomotor disturbance. He believed that petit-mal epilepsy could be detected by this method better than by hyperventilation.

Sjaardema[31] has stated that under sedation many abnormalities not otherwise recorded can be detected. He has found that Nembutal,® Seconal,® and paraldehyde often obscure patterns by producing rapid activity. Chloral hydrate gave better results used in 10 per cent solution in syrup, one to four drams orally. He found the best sedative to be Demerol® administered intravenously and followed by sodium pentothal until rapid activity begins. This combination has an effect similar to that of going to sleep and coming out of sleep. Bottle feeding may also induce first alertness and then drowsiness characterized by a pattern of four cycles per second in which focal and unilateral lesions may be detected.

Sjaardema observed that there is no unanimity in the interpretation of electroencephalograms of young children. It would seem that better knowledge of the use of sedation and further review of the criteria for abnormality in the readings are necessary before statistical analyses can have real meaning. For example, of 33 children born with erythroblastosis at Children's Hospital in Los Angeles 25 had some neuromuscular handicap, but in 15 of these children no abnormality was detected by electroencephalogram even though 10 of the 15 were given sedation. Such results do not seem conclusive.

5. *Early Treatment of Neuromuscular Handicap*

A very young infant that does not spontaneously lift his head when in the prone position may be helped to develop this faculty by leaving him on his abdomen for gradually increasing periods of time. Head and trunk control may be developed in a child six to twelve months of age by propping the child in an almost sitting position, asking him to

put out his hands and grasp one's thumbs, and pulling him forward to a sitting position on the edge of his seat, from which he can be assisted to stand on the therapist's lap. A child who does not kick his legs alternately in the normal manner may be trained by exercise of the bicycle type. Many other devices, such as special chairs adapted to particular handicaps and special jumper seats on springs, are being improvised to help the palsied infant to develop at as nearly normal a rate as possible.

6. *Mental and Personality Development*

Berenberg, Byers and Meyers[5] have stressed the importance of promoting maximum personality adjustment as well as physical potential. They point out the well-known socializing influence of the nursery school in its "effect of weaning from close parental control, the relieving of the overtaxed parents and siblings of caring for a child through an unusually long period of dependence," as well as the assistance that can be given the parents by teaching them new methods of dealing with the child's handicap.

McIntire[19] reported that of a series of patients with cerebral palsy 75 per cent were of average intelligence. Hohman,[15] however, reported an exactly reverse proportion in a review at the October 1952 meeting of the American Academy of Cerebral Palsy: 75 per cent of his patients were below average in intelligence, and of these 50 per cent were seriously retarded. Miller and Rosenfield[21] tested 330 children in Buffalo who were under treatment for cerebral palsy and found that 50 per cent had an intelligence quotient below 70, 22.5 per cent were rated between 70 and 89, 23 per cent between 90 and 109, and 4.5 per cent over 110. They found that 40 per cent of the spastic children and the same proportion of those with athetosis were very distractable, and that 40 per cent of the spastic children and 8 per cent of those with athetosis had disturbances of visual control. Of 954 palsied children in Los Angeles County[32] 46 per cent were found to have normal intelligence, only 4 per cent being above average while 21 per cent were on the borderline of normal and 29 per cent had low mentality.

Emotional disturbances, behavior problems in school and retardation in learning have been attributed by Seldowitz and Berman[30] to "crossed laterality"—a condition in which the dominant eye is contralateral to the preferred hand. Special training methods to overcome this handicap have been very successful.

7. *Orthopedic Surgery*

Barnett[3] reviewed orthopedic surgical procedures in relation to cerebral palsy recently and concluded that operation "is only one part of a broad plan of treatment for patients with cerebral palsy; the aim of treatment is to make the patient physically independent and socially competent and acceptable. Although surgery is often required to supplement specific therapies and bracing, it is not to be considered as a substitute for other rehabilitative measures. The value of surgical treatment should not be measured by its aid in overcoming a local deformity or obstruction, but by its contribution to the overall rehabilitation of the patient. A knowledge of proper indications for surgery and adequate preoperative and postoperative care is as essential for good results as a skillful performance of the surgical procedure." Among the common deformities associated with cerebral palsy he included progressive subluxation and dislocation of the hip joint, which was also reported from the Children's Hospital in Los Angeles.[18] If such subluxation seems imminent because of marked adduction deformity, frequent hip x-rays are indicated to detect the earliest stages of subluxation so that surgery can be planned in an effort to prevent further migration of the head of the femur.

8. *Neurosurgery*

Rand,[27] in a recent discussion of the problem and review of the results in the literature, called attention to the fact that in a series of 17 cases of seizures thought to be produced by birth injuries, 76 per cent were relieved from seizures by ablation of the focal epileptogenic lesions of the cortex. Coincidentally with the diminution of seizures, in hemiplegic patients the muscular handicap decreased and behavior improved. Penfield[24] stated that "operative procedures are better controlled and are less subject to risk at 10 years than at 2 but we have been forced to reconsider our policy of postponement in regard to radical ablation of the epileptogenic cortex in those cases in which there is progressive intellectual degeneration or progressive paralysis."

In 40 per cent of palsied children with abnormal behavior electroencephalograms indicate abnormality. Some of these patients respond to drug therapy. Those with most severe emotional disturbance may not, and neurosurgical operation may facilitate general care and rehabilitation. Frontal topectomy, cingulate gyrectomy or prefrontal lobotomy is suggested.

9. *Drug Therapy*

Drugs which reduce or control seizures are important in the treatment of cerebral palsy, since seizures often occur in this condition. For example, in a recent survey in Los Angeles County[32] seizures were noted at some time in 37 per cent of 1,287 cases; 33 per cent of the patients with athetosis, 62 per cent of the spastic children, 40 per cent with mixed symptoms and 42 per cent with rigidity were reported to have had seizures of some kind.

Bradley[6] has pointed out the value of Benzedrine®

and Dexedrine® in behavior disorders in children. Behavior disorders occur very frequently in palsied children, even those in whom no abnormalities are indicated by electroencephalography; these drugs in doses of 5 to 20 mg. a day sometimes afford considerable improvement in behavior.

Improvement in behavior can be obtained in some cases by the use of certain other medication such as Tridione® in doses of 0.3 gm. (5 grains) three times a day or Dilantin® sodium in doses of 32 mg. (½ grain) one to three or more times a day. This improvement may be of a spectacular nature, as in the case of a four-year-old boy who, after study and treatment at the School for Cerebral Palsied Children of Southern California was referred to the local school but could not be managed there. He was given 5 mg. of Benzedrine sulfate daily, and with this medication he has been able to adjust to the local school group.

Alcohol is still probably the best relaxant for cerebral palsy patients, especially those with athetosis, and paraldehyde is sometimes effective. Phenobarbital and Mebaral® have been used with success, the latter especially in tension athetosis in doses up to 0.59 gm. (9 grains) daily. Chloral hydrate in 10 per cent syrup given orally or in 10 per cent aqueous solution given rectally may be used for occasional sedation if other drugs fail to produce sleep.

644 North Central Avenue.

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Western Equine Encephalitis in Infants

A Report on Three Cases with Sequelae

HENRY B. BRUYN, M.D., San Francisco, and
EDWIN H. LENNETTE, M.D., Ph.D., Berkeley

• Approximately one-third of the laboratory-confirmed cases of Western equine encephalitis occur in children under the age of 10. The present paper describes three instances of Western equine encephalomyelitis virus infection in infants under one year of age, together with the resultant sequelae. The difficulties associated with diagnosis of central nervous system disturbances in very young children are discussed, and it is pointed out that in view of the frequent occurrence of clinical infections with the arthropod-borne encephalitis viruses these agents should be given serious consideration as a cause of acute central nervous system infection in childhood and as the possible etiology for obscure, severe neurological disturbances in the pediatric age groups.

SINCE THE ISOLATION and identification of the Western equine encephalomyelitis virus from horses by Meyer in 1931[6] and the development of serologic methods for determining the etiologic factor in cases of human infection, much epidemiologic information on the disease has accumulated. It has become apparent that in California this virus, as well as that of St. Louis encephalitis, is a frequent cause of the clinical entity "infectious encephalitis"[5] and that the geographical and seasonal distribution of human cases of Western equine encephalitis seems to be directly related to the environmental requirements of the arthropod vector, the mosquito Culex tarsalis.[4]

In the eight-year period 1945 through 1952, 1,985 cases of "infectious encephalitis" were reported to the California State Department of Public Health.[1] The year of highest incidence was 1952 with a total of 752 cases reported. In the seven years 1945-1951, 196 cases of Western equine encephalitis were confirmed by laboratory means, and in the year 1952 alone there were 370 laboratory proved cases (Table 1).

Epidemiologic studies of the laboratory-confirmed cases of virus encephalitis in California indicated that this disease is particularly frequent in the younger age groups. Lennette and Longshore[5] reported that of a total of 135 cases of St. Louis encephalitis occurring between the years 1945 and 1950, 38 (28 per cent) were in persons under 10 years of age, and 31 (40 per cent) of 77 cases of Western equine encephalitis were in persons in that age group. In 1952, of a total of 370 laboratory-confirmed cases of Western equine virus infection, 178 or 48 per cent were in persons under the age of 10 years. The proportion of cases of Western equine encephalomyelitis for the period 1945 through 1952 in which the patient was under 10 years of age is shown in Table 1. More than one-third of the laboratory-confirmed cases since 1945 have been in persons under the age of five years and approximately one-half in persons under the age of 10. Patients with St. Louis encephalitis in the same period were not of the younger age groups in so high a proportion of cases. It was suggested[5] that one reason for this might lie in a higher incidence of inapparent infection with the St. Louis virus in the general population of the endemic area which in turn could result in a high proportion of infants with passively acquired immunity.

While the severity of a disease may be reflected in the mortality rate, it may also be reflected in the development of serious sequelae which, over a period of time, may present highly important socio-economic problems. The incidence of sequelae in instances of human infection with the virus of Western equine encephalitis cannot be stated at present. This information will be acquired only after long-term study of large numbers of patients with labora-

TABLE 1.—*Age distribution of laboratory-proved cases of western equine encephalitis, California, 1945-1952*

Age Group	1945-50 No. Cases	1945-50 Per Cent of Total	1951 No. Cases	1951 Per Cent of Total	1952 No. Cases	1952 Per Cent of Total
Under 5 years.....	61	35	12	55	147	40
Under 10 years....	77	44	13	59	178	48
Total, all ages....	174	100	22	100	370	100

Source: California State Department of Public Health.[1]

From the Division of Pediatrics, University of California School of Medicine, San Francisco (Bruyn), and the Viral and Rickettsial Disease Laboratory, California State Department of Public Health, Berkeley (Lennette).

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tory-confirmed infection. Such studies are at present in progress under the aegis of the California State Department of Public Health. Undoubtedly there are many instances of illness due to this virus in which the clinical symptoms are not those of an encephalitic process and laboratory confirmation therefore is not obtained. Until such time as the more common use of serologic tests in such cases brings to light the varied potentialities of the clinical syndrome of infection with this virus, the true incidence of sequelae will be difficult to ascertain. It is apparent, however, from the literature, that there occurs an appreciable incidence of serious neurological damage in children following viral encephalitis of several etiologic types, including that due to the Western equine virus. Wynns and Hawley,[9] dealing with St. Louis encephalitis, reported a mortality rate of 62 per cent in children, with neurological sequelae present in 22 per cent of the survivors. They noted that the incidence of permanent sequelae was highest in the younger age groups. Farber and co-workers[3] described eight cases of Eastern equine encephalitis in infancy; five patients died and the three survivors had permanent neurological sequelae. Simpson and Meiklejohn[8] examined 38 patients who had had Japanese B encephalitis one year after onset of the disease and noted sequelae in 11 of them, 10 of whom were under the age of 15 years. Reports of residual neurological damage following infection with Western equine encephalitis virus have been limited to descriptions of specific cases. Davis[2] reported two cases in early infancy with permanent sequelae in both. Noran and Baker[7] described one case occurring at the age of one month, with permanent neurological damage of severe degree and death at the age of three years.

It is the purpose of the present report to present three instances of permanent and serious neurological sequelae of Western equine encephalitis virus infection occurring in children under one year of age. The three patients were studied at the University of California Hospital and the diagnosis was confirmed by laboratory tests at the Viral and Ricksettsial Disease Laboratory of the California State Department of Public Health in Berkeley.

CASE REPORTS

CASE 1: A 10-month-old girl was admitted to the University of California Hospital on October 6, 1949, with complaints of convulsions and high fever for eight weeks. At the onset of illness mild diarrhea developed, and on the second day of illness, fever, as high as 108 degrees F., which continued for ten days. On the second day of fever, convulsion that lasted 24 hours occurred. The patient was then treated in a hospital for a week. At the time of discharge she was mentally disoriented and the right arm and right leg seemed weak. Fever continued and convulsions occurred at least once a day. A variety of diagnoses had been considered, including tonsillitis, infection of the ear, measles and pneumonia. The convulsions were ascribed to the fever.

TABLE 2.—*Results of laboratory tests on patient in Case 1, a girl, 10 months of age

Test Antigen	Type of Test and Results: Complement Fixation	Neutralization	Hemagglutination-inhibition
Western equine encephalitis	< 1:8	300 LD_{50} or >†	.....
St. Louis encephalitis	< 1:8	.....	.....
Mumps	.....	.....	1:16‡
Q fever	< 1:8	.....	.....

*Onset of illness in July 1949; blood specimen examined taken on October 7, 1949.

†Serum neutralized 300 or more 50 per cent mouse lethal doses of virus—a high titer.

‡Not diagnostically significant.

The family had been living in an agricultural community in Yolo County during the six months preceding the onset of illness.

The child, on admittance to the University of California Hospital, had a high pitched cry and her back hyperextended. The hands were clenched in tetanic fashion. Reflexes were equal and hyperactive. Babinski's reflex was evoked bilaterally.

The numbers of cells in the blood were within normal limits. The sedimentation rate was zero. No abnormalities were noted in the urine. The spinal fluid pressure was 20 cm. of water. No cells were observed in a specimen of spinal fluid and results of chemical studies were normal. The result of a toxoplasmin skin test was negative. Specimens of blood from the mother and infant for examinations for toxoplasmosis were sent to the Army Medical Service Graduate School in Washington, D. C., and were reported as "negative."* Specimens of blood from the patient were also sent to the California State Health Department's Viral and Rickettsial Disease Laboratory in Berkeley for study. The results of the viral tests are summarized in Table 2. The patient's blood had the capacity to neutralize 300 or more lethal doses of the Western equine encephalomyelitis virus. No blood could be obtained from the patient's mother for testing to rule out completely the possibility that the antibody in the child had been acquired by transplacental passage. While antibody titers of this magnitude have been observed by one of the authors (E.H.L.) in adults residing in areas where Western equine encephalomyelitis virus infections are endemic, it seems unlikely that passively acquired antibody would be present in such strength after 10 months. It is considered reasonable, therefore, to relate the child's antibody titer to the present illness. The fact that no complement-fixing antibody was demonstrable is not necessarily at variance with such an interpretation, since large-scale studies now under way in the Viral and Rickettsial Disease Laboratory show that complement-fixing antibody may appear quickly, reach a peak rapidly, and then decline or disappear after a variable, but brief, period.

No abnormalities were noted in x-ray studies of the chest. A pneumoencephalogram showed the ventricles to be symmetrically dilated, without displacement or block. The changes observed were ascribed to atrophy of the brain.

The temperature ranged between 37 degrees C. and 39 degrees C. and gradually became more stable around 37 degrees C. Episodes of spasms and convulsions became less frequent. At the time of discharge from the hospital, October 20, 1949, the patient seemed to respond to the voice of her parents and the nurses.

Psychometric studies carried out before discharge showed

*The authors are indebted to Dr. Joel Warren for conducting these tests.

a mental age of 6 months, and an intelligence quotient of 56. The child was socially responsive but did not voluntarily attempt to reach for moving articles. The psychometric studies were repeated six months after discharge, approximately eight months from the onset of disease. At this time the child showed a great deal of improvement in understanding words and in designating familiar objects. She was graded as approximately one year in mental age, representing a six-month gain in mental age in the interval since discharge.

The child was referred to the Cerebral Palsy Program through the Crippled Children's Service of the California State Department of Public Health and was accepted for aid.

Second admittance to hospital. The patient was admitted to the hospital March 17, 1952, referred from a hospital in the Central Valley where she had been hospitalized because of persistent convulsions of "unknown etiology." The child had continued to show improvement. She was able to close and open her hands but seemed to have difficulty in releasing objects. She was able to move her arms with poor control—the left better than the right. She could move both legs, the left better than the right, but was unable to walk. She was unable to sit up. There was some control over bladder and bowel function. She had difficulty in chewing but none in swallowing. She was able to say a few words, but no sentences.

The head was extremely small—45 cm. in circumference. There was asymmetry of the right occiput. Flexion spasticity of both arms was noted. The reflexes were normal. There was spasticity of the right leg. The feet were held in equinus position.

Electroencephalograms showed no dysrhythmia or focal change. Pneumoencephalography on March 19, 1952, showed well-filled ventricular system and subarachnoid channels, without displacement. The lateral ventricles and subarachnoid channels were larger than normal but relatively less so than in the pneumoencephalogram taken in October, 1949.

The procedure was done with the patient under ether anesthesia. Following removal of spinal fluid and introduction of air, cardiac and respiratory activity ceased.

Postmortem examination was carried out at the Coroner's office, City and County of San Francisco.*

There was foamy blood in the right ventricle and right auricle of the heart. The brain appeared edematous. Air bubbles were seen throughout the leptomeningeal vessels. On palpation firm, ill-defined nodules were noted in the gray matter, most prominent in the left mid-cortical region. There was thickening of the floor of the left lateral ventricle and adhesive bands in the third and fourth ventricles. Multiple sections revealed firm, pale sclerotic areas measuring 1 to 2 cm. in maximum diameter in both basal ganglia, in the subcortical white matter of the left parietal lobe, and in the right temporal lobe. There was disruption of the normal architecture of the pons. The cerebellar hemispheres showed pronounced sclerotic involvement of the white matter and the dentate nuclei. The spinal cord was macroscopically normal.

Upon microscopic examination, scattered small areas of degeneration and glial proliferation were observed throughout the cerebrum. In some areas perivascular lymphocytic reaction was present. Focal accumulations of macrophages were observed in areas of a basophilic staining material, presumably calcium. In the cerebellum some loss of Purkinje cells was noted. There was congestion in the brain stem and spinal cord.

CASE 2: The patient, a boy one month of age, was first admitted to the University of California Hospital July 6, 1950, with complaint of muscular spasms for the past 36 hours.

The illness had begun with the appearance of irritability and diarrhea. About 12 hours after onset of diarrhea, the child became rigid, with arms flexed and legs hyperextended. This lasted for several minutes. Similar episodes occurred frequently despite sedation. There were no clonic movements, no periods of apnea, and no cyanosis. The temperature fluctuated between 102 degrees F. and 104 degrees F. On the afternoon before admittance, a single dose of streptomycin was given on the assumption of a diagnosis of meningitis, due to *Hemophilus influenzae*. Leukocytes at that time numbered 8,000 per cu. mm. of blood.

The child had lived in Merced County before admittance to the hospital.

Upon physical examination the patient was observed to be lying limp and with the head turned to the right. The neck and back were not stiff. The reflexes were normal. The diagnosis on admittance was meningitis of unknown cause, probably bacterial.

Leukocytes numbered 7,600 per cu. mm. with 80 per cent polymorphonuclear cells. No growth occurred on cultures of the blood.

The spinal fluid was faintly turbid and contained 270 cells per cu. mm., of which 54 per cent were lymphocytes. The reaction to a Pandy test was 3 plus; the glucose content was 52 mg. and the protein content 150 mg. per 100 cc. No organisms grew on a culture of the fluid.

The results of serological tests for neurotropic viruses are given in Table 3, which shows that antibodies against Western equine encephalomyelitis virus appeared during the illness. No antibody was detected in the mother's blood, which indicates that the patient acquired antibody through active infection, and not passively from the mother.

The temperature ranged between 38 degrees C. and 39 degrees C. for the first five hospital days, following which it remained normal. A second specimen of spinal fluid was aspirated on the third hospital day. The leukocyte content was 370 per cu. mm., 90 per cent of which were lymphocytes.

By the sixth hospital day, the convulsive episodes had become less frequent and by the 16th hospital day the patient seemed considerably improved. Fluid withdrawn by cisternal puncture contained 30 cells per cu. mm., all lymphocytes; the protein content was 136 mg. per 100 cc. The patient was discharged.

Psychometric examination when the patient was two months of age showed development to a stage considered normal for infants 4 to 8 weeks of age. The results indicated definite improvement over examination shortly after admittance to hospital.

The child was examined again five months after the onset of illness and development was almost normal in all areas but gross motor abilities. There was a distinct interference in coordinated activity of arms and hands.

Upon physical examination 11 months after the illness, hyperactivity of reflexes of the left leg was noted. There was tension of the hands, in which effort seemed to impair achievement in picking up objects. A psychometric examination showed adaptive behavior at a level of 28 to 32 weeks, language behavior at 28 weeks, and personal-social behavior at 28 to 32 weeks. At a chronological age of 12 months, the development quotient was approximately 60.

The patient was admitted again on October 4, 1951. The complaint was a convulsion the day before admittance. This convulsion seemed to progress from left cheek to the left leg, and eventually included the whole body. There was moderate cyanosis. The episode lasted approximately four hours.

The patient was well-developed and well-nourished but seemed tired and irritable. The head was 43.5 cm. in circum-

*The authors are indebted to Dr. Henry Moon for permission to present the pathologic findings.

TABLE 3.—*Results of laboratory tests on patient in Case 2, a boy, 1 month of age, and on patient's mother*

Type of Test	Dates on Which Blood Specimens Were Taken and Results of Tests				
	Patient*				Mother of Patient
	July 11, 1950	July 21, 1950	Aug. 3, 1950	Oct. 5, 1951	July 28, 1950
Complement fixation					
Western equine encephalitis	< 1:8	1:64	1:256	1:64	< 1:8
St. Louis encephalitis	.....	< 1:8	< 1:8	< 1:8	< 1:8
Lymphocytic choriomeningitis	.....	< 1:8	< 1:8	< 1:8	< 1:8
Mumps	< 1:8	< 1:8	< 1:8	< 1:8	1:8
Neutralization					
Western equine encephalitis	400 LD_{50}	.....	5,000 LD_{50}	1,100 LD_{50}	Negative
St. Louis encephalitis	.....	.....	Negative	Negative	Negative

*Onset of illness July 4, 1950.

ference—small for a child 15 months of age. The reflexes were hyperactive bilaterally.

The diagnosis on admittance was postencephalitic convulsive state.

There were no cells in the spinal fluid, and glucose and protein contents were within normal limits.

Electroencephalography showed consistently higher than normal potential with greater abnormality on the right side of the head. These findings supported clinical evidence of a right hemispheric lesion. Upon pneumoencephalographic examination it was noted that the right lateral ventricle and third ventricle were slightly dilated. The subarachnoid channels on the right side were accentuated and enlarged. The impression was that of cerebral atrophy on the right.

Phenobarbital was administered, 15.0 mg. three times a day. Convulsive episodes occurred on two occasions, in each instance associated with fever of known cause.

The patient was examined again two years after the onset of the original illness. He was walking awkwardly and seemed to have a tightness in the left hand. Hyperactive and inattentive, he jumped about on the floor in a leapfrog fashion or banged objects noisily and gleefully responded to the racket. There was no interest in sustained or associative play. Upon psychometric examination the mental development was observed to be that of a normal child about nine and a half months of age and the intelligence quotient was about 40.

Reexamination approximately two and one-half years after onset of disease showed no change from the previous study. By psychometric evaluation the child was determined to be at "imbecile" level of function. Application had been made for placement in an institution.

CASE 3:* A seven-month-old white girl was admitted to the University of California Hospital in December 1952. The complaint was convulsions.

In June 1952 the patient had had a temperature of 102.6 degrees F. and was moderately sick. There were no positive physical findings and no specific therapy was prescribed. The patient was examined again by the same physician the following day and, except for high fever, no definite symptoms or physical findings were noted. Two days later the baby suddenly had a convulsion. Lumbar puncture was carried out and the spinal fluid contained 1700 leukocytes per cu. mm. A diagnosis of encephalitis was made, principally on the basis of the increased incidence of the disease at the time and also because the parents reported that the child had been bitten by a mosquito shortly before the illness began. A horse on a neighboring ranch was known to have died of encephalitis in the previous month.

*This case is presented through the courtesy of Dr. George H. Schade.

TABLE 4.—*Results of laboratory tests on patient in Case 3, a girl, 7 months of age, and on patient's mother*

Type of Test	Dates Blood Specimens Taken, and Results of Tests		
	Patient*		Mother of Patient
	Dec. 22, 1952	Mar. 2, 1953	April 6, 1953
Complement fixation			
Western equine encephalitis	1:1024	1:512	< 1:8
St. Louis encephalitis	< 1:8	.....	< 1:8
Mumps	< 1:8	.....	< 1:8
Neutralization			
Western equine encephalitis	1 million LD_{50}	.....	100 LD_{50}

*Onset of illness June 30, 1952.

There were frequent major convulsive seizures for several days. Improvement was then rapid and the patient was considered well after seven days.

Thereafter the baby developed slowly. At about six months of age, she began to have sudden dropping movements of the head with sharp jerks of the arms and uprolling of the eyes. The mother said the baby did not seem alert.

On physical examination there was no evidence of abnormality of the head. The reflexes were normal, but the motor tone was poor. Moro reflex was equal and hyperactive. During the examination, several swift convulsive seizures of major intensity were observed.

Electroencephalogram showed both generalized and focal paroxysmal dysrhythmia of a wave and spike type. The focal change was in the frontal half of the right hemisphere. The interpretation was "severe cerebral dysfunction of the convulsive type." The abnormality noted was similar to that described in encephalitis of some types.

Psychometric examination showed development that would be normal at approximately six weeks of age, with a developmental quotient of 21. Virologic tests of the blood were carried out. The results are given in Table 4. Strong complement-fixation and an extremely high level of neutralizing antibodies to the Western equine virus were observed. The high titer of complement-fixing antibodies in the child, and absence of them in the mother, together with a neutralizing antibody level 10,000 times that found in the mother, indicated that the patient was actually infected with the Western equine virus, and did not acquire antibodies passively.

The diagnosis was postencephalitic convulsive state, with lightning major seizures and severe mental retardation.

DISCUSSION

The three cases described illustrate the severe neurological damage that may result from infection with the virus of Western equine encephalitis in early childhood.

In the first patient, the prolonged febrile period, lasting about eight weeks, suggests that prolonged fever may constitute a possible diagnostic clue in central nervous infection of this type. The persistent fever may also have contributed to the damage in the brain. The convulsions, which were initially ascribed to the high fever, also represent important diagnostic clues, which should be considered a definite indication for lumbar puncture. The improvement noted in the patient over a period of over two years is manifest not only in the psychometric tests but also in the comparison between the two pneumoencephalograms. Nevertheless, at the time of her death, which cannot be ascribed to encephalitis, she represented not only a serious problem for her immediate family but also a long-term problem for a number of public and private agencies. The pathological findings in this patient are of interest inasmuch as they are compatible with either a neurotropic virus disease or toxoplasmosis. The latter disease seems to be unlikely in view of the negative results of serological tests on both mother and infant and, in the patient, the negative reaction to a skin test and the normal optic fundi. Furthermore, the findings in the brain are essentially similar to those described by Noran and Baker[7] in a case of Western equine encephalitis as well as to those reported by Zimmerman[10] in cases of Japanese B encephalitis. The observation of focal sclerotic areas especially resembles the findings described by Zimmerman. The observation of deposits of calcium salts was reported by Noran and Baker and was stressed by Zimmerman. These investigators were describing material from cases in which, as in the present case, death took place long after the acute stage of disease.

Case 2 illustrates the problems of diagnosis that may be encountered in the early stages of the disease. In this case it seems quite possible that the short febrile period could have been ascribed to a successfully treated bacterial infection, in which the causative organism was not identified because an antibiotic was used before material for cultures could be obtained. The serological diagnosis in this case was enhanced by obtaining a blood specimen from the mother, which showed the absence of antibody. It was thus possible to assume that the antibody found in the specimen taken from the patient had been acquired since birth and not by passive transfer through the placenta. The pneumoencephalographic evidence of a focal destructive process correlated well with the clinical observation of early stiffness in one leg and of the nature of the convulsions. The child represents a very difficult problem for the parents to handle and will be under custodial care of the state indefinitely.

Case 3 also is illustrative of difficulties that obscure the diagnosis. The eventual solution resulted from the application of viral diagnostic tests in a case of "convulsions of unknown cause."

From the small amount of information available in the published literature, and with the cases here reported as further evidence, it appears that Western equine encephalitis may by no means be a rare cause of serious neurological damage in childhood. With the increased number of cases of human infection with this virus in 1952, and the expectancy that cases of this disease will continue to occur, physicians in California should give serious consideration to this virus, not only as a cause of acute central nervous system infection in childhood, but also as an explanation for obscure, severe neurological disturbances in the pediatric age groups.

1392 University Avenue, Berkeley.

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The Management of Strabismus

ARTHUR JAMPOLSKY, M.D., San Francisco

• The original causes of strabismus and the complications that develop from efforts by a child to adjust to the condition may present a complex diagnostic and therapeutic problem. The complications of suppression, amblyopia, contractures and anomalous visual habits may become more difficult to correct than the cause of the strabismus. The longer the duration of strabismus, the more complex the problem, the more difficult the treatment, and the less the probability of functional cure. Treatment should be started early. Correction may be brought about by the use of glasses, eye patches and orthoptic training, or by operation. If anatomic abnormality prevents bringing the eyes into line by conservative means, operation should be carried out after the best results possible by these means have been achieved. Surgical treatment, too, where it is indicated, should be done early, in order that normal binocular cooperation can develop before abnormal visual habits can become established.

REQUISITE TO SECURING good binocular vision in children is to obtain a clear retinal image focused in each eye and to get the two eyes working together as a team during the formative years of visual development. Without good vision and straight eyes there is little opportunity for development of good visual habits. The longer the delay in the treatment of strabismus, the greater the departure from physiological development and the less chance for functional cure.

Physicians consulted by the parents of children with crossed eyes must be prepared to give logical answer to questions such as: What causes the eyes to cross? Will the child outgrow the condition? How long must one wait before treatment? Is the condition hereditary? Will glasses or television weaken the eyes? What about wearing a patch over one eye? Will eye exercises help? Is an operation necessary?

In order to understand the various factors involved in these questions and to appreciate the necessity for early treatment, the physician must be grounded in the principal causes of strabismus and have working knowledge of the complications that follow and of the means of treatment.

VISUAL DEVELOPMENT

Not infrequently during the first six months of life the eyes may wobble a bit and not work in perfect cooperation. With the development of good binocular reflexes, the two eyes should work together well by the time a child is six months of age. If they do not, the cause must be determined. An eye that is *constantly* crossed and remains so, even during the first few months of life, should be examined without delay. It is in the first six years of life that a child develops vision and learns to use the two eyes together. If the images in the two eyes are correctly in focus and the eyes are correctly aligned, then good visual cooperation will stabilize well by the age of six years. But during this period a child may just as easily learn bad habits of vision and stabilize the use of the two eyes together in the crossed position. The resulting poor vision and stabilized bad habits of ocular cooperation may become unchangeable once the formative period of visual development has passed, for concomitantly a host of other complications are developing—localized in the form of extraocular muscle contractures, and cerebral in the form of anomalous visual reflex patterns.

Do some children outgrow strabismus? Contrary to popular belief, few children outgrow constant strabismus. Those who do so may have cosmetically straight eyes but poor vision in the formerly crossed eye. Visual impairment of this kind may be prevented if treatment is begun before visual habits and the previously mentioned associated changes are so firmly established that there is little possibility the patient will ever develop the ability to use clear-visioned eyes together.

Although many parents seem reluctant to accept them, it is better that they be told the facts and that treatment be started early to secure normal stabilization, by whatever means necessary, lest the possibility of obtaining functional as well as a cosmetic cure be greatly diminished.

From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine.

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CAUSES OF STRABISMUS

Strabismus is caused by anomalies of anatomy, of innervation, or of fusion.

Anomalies of anatomy. Correct alignment of the eyes may be impeded by weak or overacting muscles, failures in muscle development, malformed orbital structures, or contractures of ocular muscles or trauma. During the period of development any anatomical situation that prevents the eyes from pointing straight ahead naturally impedes the development of normal binocular cooperation.

Anomalies of innervation: Farsightedness, excessive convergence. Farsightedness is the principal cause of convergent strabismus in the two- to three-year age group. A farsighted child in an effort to obtain clear retinal images in each eye must make a focusing effort with the muscles of accommodation. Such an effort induces a reflex stimulation to convergence of the eyes. The effort made by a child with anatomically straight eyes to overcome farsightedness in order to obtain clear vision, may cause the eyes to cross. Such a child, if his innate binocular cooperation is strong enough, may "back up" his visual axes and realign them in the straight-ahead position despite the continued focusing effort. Such a status is a precarious one, requiring constant mental effort. The strabismus may be held latent, and become manifest only during periods of fatigue or illness when the child cannot make the effort necessary for stabilization. Such factors as measles or mumps, or debility following trauma or severe emotional upsets, may be precipitating factors but not the cause of strabismus. Glasses, perhaps used only temporarily, may cure such a case of strabismus. The glasses instead of the eyes do the focusing, and the need for effort to hold the eyes straight and clearly focused is eliminated. With growth and stabilization of such a situation, the temporary glasses may be discarded. If this simple means of correcting strabismus of this type is not used or is delayed and constant strabismus results, the host of visual complications that immediately develop may never completely and satisfactorily be eradicated.

For reasons not entirely clear, excessive ocular convergence existing usually in some hyperkinetic children, is sometimes the basis for the strabismus.

Anomalies of fusion. The inability of the brain to blend the images from each eye into a unified picture by a process called fusion may be the basis of strabismus even in eyes that are at first relatively straight and clearly focused. Normally, the innate potential for using the two eyes together must be augmented by the actual learning process of seeing clearly and by securing binocular cooperation early. In the presence of strabismus, the fusion ability may develop in such a way that stable use of the two eyes together in the crossed position becomes firmly established and difficult to reverse.

Hereditary factors are of considerable importance in any of the previously mentioned causes of strabismus and may be manifest in anomalies of anatomy, innervation, or fusion.

COMPLICATIONS OF STRABISMUS

The complications of strabismus—suppression, amblyopia, contracture and anomalous retinal correspondence—begin as soon as the eyes are constantly crossed and become continuously more firmly imbedded so long as the eye remains crossed. The complications, rather than the original cause, may become the more difficult problem in treatment.

Suppression. A crossed eye is not a "lazy eye." It is an actively ignored eye. Whereas an adult if an eye becomes crossed is constantly annoyed by the resultant diplopia, a child in the visually formative years may easily ignore it. The child immediately and continuously suppresses the lesser of the two images transmitted. This is an active inhibition, a learned cerebral process, and the longer it continues the greater the loss of visual acuity in the crossed eye.

Amblyopia. The macula of the crossed eye in unilateral strabismus cannot and does not receive the same clear image as the straight eye and therefore cannot and does not develop clear vision as long as the eye remains crossed. Moreover, whatever good vision has already developed is soon erased from the mind's eye.

Contractures. The moment an eye is crossed, the extraocular muscles are subjected to the same laws of physiology that apply to muscles in a severely and continuously flexed limb. Contractures of the striated extraocular muscles may occur in exactly the same fashion as contractures in muscles elsewhere. Contracture of an extraocular muscle is not an invariable consequence of a crossed eye, but it may occur if strabismus is not corrected; and if it does an operation that might have been averted becomes a necessity.

Anomalous retinal correspondence. Stable cerebral binocular cooperation in the strabismic position (anomalous retinal correspondence) may become fixed. A constant angle of strabismus in an eye with poor vision and suppression, with contracted muscle, if occurring during the period of visual development, may lead to the establishment of a stable "bad habit" of visual cooperation which may become a barrier to functional cure.

The four kinds of complications mentioned may be wholly averted with proper early treatment. With time, diagnosis of the complications and causes becomes mixed and confused, the treatment more difficult, and a functional cure less probable.

TREATMENT OF STRABISMUS

Treatment of the causes and the complications of strabismus is carried out by use of glasses, eye patches, orthoptic training, or surgical operation, singly or in combination.

Glasses. The image in each eye should be clearly in focus in order to provide adequate stimulus for fusion by the brain. Glasses alone may straighten the eyes in certain cases of strabismus by relieving an excessive focusing effort in far-sightedness, thus relieving convergence stimulation and permitting the eyes to become correctly aligned with clear images. Wearing glasses does not weaken eyes, nor can it be shown that they have any effect whatsoever upon the subsequent course of the refractive error. In strabismus, glasses are an essentially useful device to obtain a certain result and, if the refractive error is not too great, may be discarded when stable ocular cooperation has been secured. The viewing of television does not harm an eyeball, cause nearsightedness, or anatomically damage the eye. In children who are susceptible to strabismus or who have precarious binocular cooperation as evidenced by intermittent strabismus, the situation may be aggravated by fatigue, general or localized. Television, along with prolonged focusing on near objects and inadequate rest, should be regarded with any other fatiguing or debilitating condition as a possible precipitating or aggravating factor in strabismus only in susceptible children.

Patching. Putting a patch over the straight eye causes the crossed eye to see with its fovea and thus gain or regain vision. Usually a crossed eye will fixate with its fovea, regardless of the causes or the complications of strabismus, if forced to do so by total occlusion of the other eye. Less than total constant occlusion is for the most part useless. A patch used during the formative visual years may restore the vision in the crossed amblyopic eye to normal. In later years, the patch over the normal eye will restore the vision in the crossed amblyopic eye only to the point of vision it once attained during the period of development, but no more. For patching to be successful, the retinal image in the uncovered eye must be clear, aided by glasses if necessary. Success in getting young patients to wear a patch is directly proportional to the enthusiasm and persistence of the physician. He must give the parents a lucid explanation of what is being done and why, and must impress upon them the extreme importance of gaining or regaining vision during the critical formative period. In alternating strabismus, where good vision has developed in each crossed eye because each eye is used at one time or another, putting a patch over one eye and then the other alternately, is an excellent way to make the child forget the bad habits of binocular cooperation. The value of a patch therefore is threefold: to obtain and regain vision, to secure alternate fixation, and to eliminate anomalous visual habits.

Orthoptic training. Orthoptic training ("eye exercise" is the popular term) is not for the purpose of strengthening the muscles, but to help the child to unlearn bad habits of vision and to learn the normal habits of binocular cooperation. Of itself, it rarely cures strabismus and never cures nearsightedness, nor accomplishes the many wonders with which it previously has been credited. It is an adjunct in the treatment of selected patients between 5 and 12 years of age who will cooperate in the exacting procedure necessary. It is in this age group, in which strabismus usually has been present for some time, that the problem of treatment becomes more complex. Unfortunately, orthoptic training frequently has been misused in many cases of strabismus in which it should have been obvious from the outset that a cosmetic cure, and not a functional cure, was all that was possible.

Operation. Surgical operation is necessary for the correction of the anatomical elements of strabismus. The purpose is to correct the alignment of the eyes so that binocular cooperation may develop normally. Since it is desirable that the eyes be straight as soon as possible after the binocular reflexes are capable of development physiologically, surgical treatment if necessary for the alignment of the visual axes should be carried out between the first and second years of age in many cases. It should not be done, however, until after the variable elements of the strabismus have been corrected by conservative means or it has been determined that conservative treatment will not be of benefit. In cases in which it is patently impossible to secure normal binocular cooperation, the aim of operation is a satisfactory cosmetic appearance.

2400 Clay Street.

Histamine Treatment of Multiple Sclerosis

JAMES K. SMITH, M.D., Oakland, and
WALTER F. SCHALLER, M.D., San Francisco

• Histamine was administered intravenously or by iontophoresis to 19 patients with clearly established diagnosis of multiple sclerosis. In each of the three classifications of the disease (stationary, progressive, acute), no significant difference in improvement between treated and control groups was observed. (Controls were recorded cases in which treatment was identical except for histamine therapy.)

In four of seven cases of progressive disease further deterioration occurred despite histamine therapy. Of the other three patients one died a year later and another returned to hospital in three months with severe symptoms which were not relieved on further histamine treatment.

In two patients with remittent disease new symptoms (presumably caused by new lesions of the central nervous system) developed while histamine therapy was in progress.

In cases of stationary disease histamine treatment was of no benefit.

Reports are given of six typical cases in which histamine treatment was used.

AT THIS WRITING no method of treatment has been reported that is generally accepted as altering the course of multiple sclerosis. In 1936 Brickner[5] after an exhaustive search of the literature reported over 100 types of treatment. Putnam[16] and Schumacher[18] have since reviewed more recent methods of treatment. Putnam stated that "the proportion of improvement reported to follow all of the forms of treatment for which reasonably adequate data were available was almost exactly that in which the initial symptom or symptoms disappeared spontaneously, namely 48 per cent." Schumacher's review of drug therapy (1950) listed two broad categories: (1) Those treatments aimed at prevention or improvement of lesions in the central nervous system, and (2) symptomatic remedies (e.g., prostigmine, curare, etc.). In the former group he discussed vasodilators, ganglionic blocking agents, anticoagulants, circulatory stimulants, vitamins and vaccines among others. Of all these the one receiving widest attention at present is probably histamine.

The use of histamine in the treatment of multiple sclerosis was introduced by Horton and his colleagues in 1944.[10] The drug was given intravenously by slow drip once or twice daily for varying periods of time (up to several weeks), both in the hospital and to outpatients. Eighteen of 24 acute cases were reported "well" over a follow-up period of not longer than 15 months; 3 others in the acute group were "improved." Of a group of 78 chronic cases, 36 were reported improved. Abramson[1] in 1949 advocated the use of histamine by iontophoresis for multiple sclerosis, and Jonez[11, 12] in a series of articles since 1948 has reported an impressive number of cases treated by both these methods. Unfortunately these reports do not set forth clear criteria for improvement. It would seem that in many cases the patient's subjective evaluation is the principal basis for stating that a course of treatment has had a satisfactory effect on the disease process.

Two theoretical justifications are given by proponents of the use of histamine against multiple sclerosis. These rest upon two different theories regarding the etiology of the disease: (a) allergic and (b) vascular.

The theory that multiple sclerosis is a form of allergy of the tissues of the central nervous system has very few proponents even among allergists. Kennedy[13, 14] has written several papers describing clinical syndromes apparently due to allergic phenomena which resembled multiple sclerosis sufficiently closely to cause erroneous diagnoses. He emphasized their rarity, however, and there was no question that these cases could be differentiated from multiple sclerosis. However, the fact that allergic disorders of the neuraxis do exist is made much of by the supporters of the allergic etiology of multiple sclerosis. Another buttress for their position is provided by the work of Ferraro[7, 8] and others who have produced demyelinating lesions in animals by techniques of experimental anaphylaxis.

On the other hand, the question is raised quite reasonably: Why, if an allergic factor is a major cause, is there not more evidence for it in the his-

From the Veterans Administration Hospital, Oakland.

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tories of thousands of unquestioned cases of multiple sclerosis? Baer and Sulzberger[4] found the incidence of allergies in a group of patients with multiple sclerosis to lie in the high normal range. And Schumacher[18, 19] in his exhaustive review of this subject stated, "Clinical observation has not revealed a clear-cut instance of onset or exacerbation of multiple sclerosis due to known preceding contact with a substance to which the person was presumably or known to be hypersensitive."

The second theoretical reason for the use of histamine in multiple sclerosis is in its vasodilator effect. The argument is based on a twofold assumption:

1. That the acute lesions of multiple sclerosis are caused by vascular spasm, and that insofar as the vasospasm and its attendant ischemia can be relieved the symptoms are reversible.

2. That histamine causes a significant increase in the blood flow through cerebral tissue in man, and is therefore an effective weapon against the fundamental lesion—ischemia.

It is beyond the scope of this presentation to enter into detailed analysis of the validity of these assumptions, but it should be emphasized that as yet they remain only assumptions. In favor of the vascular theory of pathogenesis of multiple sclerosis is the report of Franklin and Brickner.[9] These writers observed arteriolar spasm in the retinas of 18 of 21 patients with multiple sclerosis. Improvement was reported in approximately half of these with the use of vasodilator drugs like papaverine and amyl nitrite. By extension it has been hypothecated that the lesions in the central nervous system in multiple sclerosis are due to localized vascular spasm. On the other hand Scheinker, on histologic grounds, has made a persuasive case for an opposing view, namely that vasoparalysis is the cause of the initial lesion. Equally careful workers in the field of neuropathology have looked for and failed to find any evidence that multiple sclerosis is exclusively or even predominantly vascular in origin.

The question of the action of histamine on cerebral blood flow must likewise be regarded as still open to debate. There is no doubt that use of the drug effects a flushing of the skin accompanied in many cases by headache. Moreover, Weiss and co-workers (1932) observed that a rise in spinal fluid pressure (presumably due to vasodilatation) occurred within a few seconds after intravenous injection of histamine in man.[21] In the same report they stated that histamine infusion produced in the exposed brain of patients undergoing operation a flushing of the pial vessels, increased amplitude of brain pulsation, and visible swelling of the brain surface. The transitory character of these phenomena was emphasized. Within three minutes the appearance had reverted to normal although the drug was still being given. The retinal vessels were also examined during histamine infusion and no change in their caliber was detected. This is in harmony with the findings of other observers that histamine may act as a dilator on some vessels and as a constrictor on others.[17] Weiss concluded that a transient dilation took place in the cerebral blood vessels, but that the drug was converted into an ineffective or inert substance very shortly after injection into the blood stream. Tucker and co-workers[20] studied the cerebral blood flow in nine cases of multiple sclerosis before and during administration of histamine, using the nitrous oxide technique of Kety and Schmidt. They found a fall in mean arterial blood pressure and a decrease in cerebral vascular resistance, but no associated changes in the cerebral blood flow beyond the extremes of normal unless associated with concomitant changes in the arterial and venous carbon dioxide content.

Alman, Rosenberg and Fazekas[3] studied the effect of histamine on cerebral blood flow in normal subjects and reported that although cerebrovascular resistance was moderately reduced during histamine infusion this was balanced by a lowering of mean arterial pressure, so that there was no significant alteration in cerebral blood flow.

To summarize, it must be concluded that thus far evidence is conflicting and opinion divided on the two questions involved: The vascular etiology of multiple sclerosis, and the effect of histamine on cerebral circulation in man.

SCOPE AND PURPOSE

The study here presented was undertaken* as a direct result of the unusual public interest aroused by the reports appearing in recent years in the lay press regarding histamine treatment for multiple sclerosis. None of the reports on this form of treatment presented adequate documentation of objective clinical signs that would enable an impartial reader to judge the value of the treatment. It seemed worthwhile, therefore, to seek evidence for such evaluation.

Histamine was administered to an unselected series of patients admitted to the Veterans Administration Hospital, Oakland, in whom a clear-cut diagnosis of multiple sclerosis seemed, to the neurological staff and consultants, established beyond question.

On reviewing recently the first 20 cases, which are the basis for this report, the authors were impressed by two facts: That new symptoms were observed in at least two patients while they were receiving daily histamine treatments, and that in four patients nervous disability progressed steadily during treatment.

*At the suggestion of Dr. Schaller.

Although intending to continue the study, the authors believe that these facts constitute an important criticism of the efficacy of the drug in the treatment of multiple sclerosis. For that reason a preliminary report is being made.

METHOD OF STUDY

The 19 patients (one admitted twice) ranged in age from 21 to 62 years. There were 18 males and 1 female; 18 white and 1 Negro. The duration of disease varied from six months to 30 years. A group of controls was established from the records of unselected patients with multiple sclerosis who had been previously studied on the same ward, receiving identical care except that they did not receive histamine.

Treatment consisted of routine ward nursing care, house diet supplemented at times by vitamins, physical therapy as indicated, and histamine medication. Some of the earlier patients in the series received histamine three to four times weekly, but the majority received it six times weekly, and in a few cases a continuous intravenous infusion was carried out for the first 48 to 72 hours. As no rapid relief of acute symptoms was obtained through the latter technique it has not been adopted as a routine. The histamine was given for the first week or two of treatment by slow intravenous drip (30 to 45 drops per minute) of histamine acid phosphate (2.75 mg.) in 250 cc. of normal saline solution, and thereafter the drug was given daily by iontophoresis by the method described by Abramson, which may be summarized as follows:

A pad of flannel is saturated with about 10 cc. of a histamine solution varied in concentration from 0.25 to 1.0 per cent according to the resultant flush obtained on previous administration. The flannel pad is applied to an arm or thigh and contact is made with an electrode of aluminum foil held by a rubber pad and strap against a flat copper plate positively charged. The other electrode is usually applied to the back, the patient lying on a table. The current is usually no faster than 8 milliamperes (average 5 milliamperes). The usual length of treatment is 10 to 15 minutes. If the patient complains of gastric distress he is given an antacid mixture before treatment.

All patients were examined by one of the authors on admission, at frequent intervals during hospitalization, and at discharge. They were rated according to the weighting scale described by Alexander,[2]* a useful multiphasic check-list for quantitative evaluation of progress. It is preferable that all ratings and examinations be made by the same physician.

An attempt was made in each case to obtain a fairly detailed history and to classify the disease as progressive or remittent. A further classification was made according to whether, in the period immediately prior to admission, (1) the disease had been stationary for some months, (2) the disease was steadily (usually very slowly) progressive, (3) acute exacerbation followed a period of remission or inactivity, or (4) the disease was improving after recent exacerbation.

*The scale lists about 45 neurological defects covering all phases of the complete bedside neurological examination and gives each point a weighted score according to the degree of severity.

TABLE 1.—Outcome of multiple sclerosis in patients treated with histamine and in control cases.

	No. of Cases*	Improved	Unimproved	Worse
STATIONARY†				
Treated with histamine	5	....	5	....
Control	7	....	7	....
PROGRESSIVE†				
Treated with histamine	7	....	3	4
Control	3	....	2	1
ACUTELY EXACERBATED†				
Treated with histamine	8	6	2	....
Control	6	6	....	....

*Twenty treated cases (19 patients) and 16 controls.
†Status of disease immediately prior to the current hospitalization.

RESULTS

The results are summarized in Table 1. The authors fully realize that this small series of 20 treatments would carry little weight in an attempt to establish the efficacy of a therapy used against a disease with as many variable factors as multiple sclerosis. However, the purpose of this presentation is not to establish a point by weight of statistics but to draw attention to the fact, as it appears, that in some cases, despite intensive histamine therapy given under hospital conditions, new lesions may develop and those already present may progress.

The first two case reports here presented exemplify the development of new symptoms during the course of daily histamine treatments. In the other cases there was measurable progression of already existent disability during the course of histamine treatment.

CASE REPORTS

CASE 1. A 24-year-old Negro male was admitted to the hospital in January 1952. He had had remittent disease since 1947 which had gradually reduced him to a paraplegic state. The disease had been stationary for six months prior to admission, when the principal finding was weakness of the lower extremities. Voluntary control of sphincters was not affected and the cranial nerves, upper extremities and cerebellum were not involved. The abdominal reflexes could not be elicited. The knee and ankle jerks were hyperactive and the Babinski sign was produced on the right side. There was some hypesthesia to all modalities of sensation below the knees. The pressure and dynamics of the spinal fluid were normal. In a specimen of the fluid one lymphocyte was observed; the protein content was 41 mg. per 100 cc.; there was no reaction to a complement fixation test, and the colloidal gold curve was 4433210000.

Histamine was given daily by intravenous drip from February 15; from March 5 to June 9 it was given by iontophoresis. On March 1, after two weeks of daily histamine injections, the patient had incontinence of urine for the first time. On examination it was found that weakness of the

right lower extremity had progressed. Within five days bladder control returned and there was no further complaint in this respect for the duration of hospitalization, nearly six months. The condition of the right leg improved more gradually over the next two to three weeks, but at the time of discharge it had not improved over the status on admission. On March 24 the patient complained of numbness of both hands. Sensory testing indicated no loss of sensitivity to pin-prick, touch or temperature, but vibratory sense was slightly diminished over the fingers of both hands and the sense of position was impaired to such a degree that when the patient's eyes were closed slight searching movements (so-called "pseudo-athetosis") of the outstretched fingers were made. This finding and its subjective component gradually subsided over the next few weeks. At the time of discharge in September 1952 the rating of the disease was essentially the same as it had been on admission.

CASE 2. A 38-year-old white male was admitted to the hospital in December 1951 with a history of remittent disease since 1945. The initial symptom was shimmering vision. (A physician who examined him at this time had noted nystagmus.) This was followed some months later by a transient scotoma in the right eye. This cleared and there were no symptoms for about three years, after which, for several weeks, the patient had dysarthria, locomotor ataxia and return of the visual difficulty. This also cleared up and he remained fairly well for two years. For a week before the present admission there were painful sensations in the legs, clumsiness of the fingers, thick, scanning speech and diplopia. On examination nystagmus on lateral gaze to both right and left was noted, and also slight clumsiness on the finger-to-nose and heel-to-knee tests; the gait was very slightly ataxic. The Romberg sign was not present. The superficial abdominal reflexes were present and there were no signs of abnormality in the pyramidal tract.

Histamine diphosphate was given daily intravenously from December 18 to January 2 and by iontophoresis thereafter. On January 10 when the patient was discharged, he was improved. The diplopia had cleared, the nystagmus was slight and unsustained, speech was almost normal, and the patient walked without obvious ataxia. Histamine iontophoresis was continued daily in the outpatient department. On January 15, after the daily histamine treatment, there was an attack of severe vertigo, nausea and marked increase in diplopia and ataxia. He was readmitted to the hospital, where he lay flat on his back unwilling to move his head because this seemed to provoke vomiting. There were gross lateral nystagmus bilaterally, dysarthria, and poor coordination on the finger-to-nose and heel-to-knee tests, symptoms previously noted, and also difficulty in starting urination and numbness over the left side of the face. There was hypesthesia to pin-prick and to cotton on the left side of the face, and the left corneal response was hypoactive—a new finding.

Histamine therapy was continued and symptoms again gradually subsided over the next six weeks. Six months later there had been no recurrence.

CASE 3. A 33-year-old veteran was admitted to the hospital in March 1951. He had had remittent disease for eight years, beginning with paresthesia of the face and hands followed later by ataxia and weakness of the lower extremities. Despite temporary improvement after each attack, other symptoms had developed—diplopia, clumsiness of the hands, progressive loss of position sense and increasing ataxia in the lower extremities. For two weeks prior to admission, the patient had noted a substantial increase in the ataxia and diplopia.

On initial examination no remarkable physical defect was observed except for the neurologic symptoms: severe ataxia of the lower extremities; clumsiness and dysdiadochokinesis of both upper extremities, worse on the left; intention tremor and past-pointing on the finger-to-nose test bilaterally; nystagmus on lateral gaze bilaterally; weak response of the right sixth nerve and subjective diplopia on looking to the right; impairment of superficial sensation of the left lower extremity and absence of vibratory sense below the hips bilaterally. All the deep reflexes were hyperactive and the lower extremities were moderately weak. There was a sustained ankle clonus on the right and the Babinski sign was present bilaterally. The patient was unable to walk on admission and required a wheelchair to get about.

Intravenous injections of histamine three times weekly were begun on March 29. Two weeks later the patient complained of increased weakness in the legs with uncontrollable flexor spasms. On reexamination, including detailed muscle testing, a significant decrease in strength of the major muscle groups of the right lower extremity was observed. For example, on admission the strength of the right iliopsoas muscle had been rated at 60 per cent of normal, that of the right hamstrings at 75 per cent, and that of the right anterior tibial muscle group at 90 per cent. On May 22 all were rated at 40 per cent. Histamine treatment was continued, but no improvement was noted until early in June when spasms gradually diminished and strength increased. Physical therapy was continued, and the patient was eventually able to walk on crutches for short distances. At the time of discharge, on June 19, however, after nearly four months of histamine therapy, there was no significant improvement over the status on admission as measured by the rating system.

In summary, there was temporary exacerbation of symptoms during the course of treatment, and although some improvement followed, it did not exceed the status on admission. The episode observed during this hospitalization resembled in many ways the exacerbations and remissions that had occurred over the eight years before this hospitalization.

CASE 4. A 26-year-old white male on admission to the hospital in October 1950 gave a history of an unremitting course of varied neurological symptoms for about 17 months prior to admission, starting with weakness and unsteadiness of gait and followed by visual blurring and bladder disturbances a few weeks later. There had been steady weakening of the legs until the patient could not walk except on crutches and with difficulty. Weakness of the upper extremities developed, and also dysarthria, dysphagia and severe incoordination and ataxia of all voluntary movement.

On admission the vision was so poor that the patient could read only headline print. There was temporal pallor of both optic discs. Lateral gaze was impaired bilaterally, and there was coarse nystagmus in both lateral and upward gaze. The tongue deviated to the right with some atrophy and furrowing of the right half of the tongue and fibrillation. Speech was slurred and scanning. The gag reflex was absent and there was occasional difficulty in swallowing. Except for weakness of the right central facial muscles the cranial nerves were intact. Both upper and lower extremities were markedly uncoordinated and ataxic. There was past-pointing and terminal intention tremor on the finger-to-nose test bilaterally. Rapid alternate movements were done very slowly and clumsily. There was severe spastic weakness of the lower extremities and some weakness of the hand grip bilaterally with mild atrophy of the intrinsic muscles of the right hand including the thenar and hypothenar eminences. The abdominal reflexes were absent throughout. All the deep tendon reflexes were very hyperactive but approximately equal. Hoffmann and Babinski signs and sustained ankle clonus were present bilaterally. No sensory abnormality was noted except for some loss of sensitivity to pin-prick over the right lower extremity. Spinal fluid was under normal

pressure and dynamics and contained 11 white cells per cu. mm., and 78 mg. of total protein per 100 cc.; results of complement fixation were negative and the gold curve was 4555321000.

Physical therapy was begun and histamine was given by intravenous drip three times weekly for a total of 20 treatments. During this period the patient complained voluntarily of increasing weakness of the lower extremities and increasing unsteadiness and ataxia, and finally asked that the treatment be discontinued since he felt that his condition was worse. On reexamination in March 1951 no new abnormalities were observed, but there had been no improvement in those noted on admission, and weakness of the lower extremities had increased so that whereas on admission the patient had been able to walk with difficulty on crutches, at the time of his discharge he was confined to a wheelchair.

CASE 5. A 31-year-old white man first had "numb feelings" of the feet ten months before admission. This symptom was followed by stumbling, ataxic gait and blurring of vision. These symptoms became steadily worse over the ensuing months, and in addition clumsiness of the left hand and finally spastic paraplegia and impairment of sphincter control developed.

He was admitted in April 1951 and remained in the hospital nearly four months until August 1951. Findings on examination included bilateral horizontal nystagmus, pallor of the left optic disc, hypalgesia over the left side of the body and the right side of the face, marked intention tremor, scanning speech, ataxia of the left upper and both lower extremities, and spastic weakness of the lower extremities. The abdominal reflexes were not elicited and the Babinski sign was present bilaterally. The spinal fluid contained no cells; the protein content was 45 mg. per 100 cc., and the colloidal gold curve was 5432100000.

Histamine was given intravenously three times weekly from April 23 to August 8. At the time of discharge there was no quantitative improvement in any of the symptoms listed above and progression in most. The degree of deterioration is indicated by the following estimates of muscle strength:

	—Percent of Normal*—	
	April	July
Left gluteus maximus	70	40
Left hamstrings	75	45
Left toe flexors	30-45	10
Left anterior tibial muscle	55	25
Left toe extensors	30-55	10-30

The clinical effect was that in the interval the major muscle groups of the left lower extremity had lost the power to move the weight of the extremity against gravity.

CASE 6. A 39-year-old white veteran was admitted to hospital in March 1951 with a history of slowly progressive disease without remission of about a year's duration, starting with weakness of the right lower extremity.

On admission there was coarse nystagmus on lateral gaze bilaterally. There was spastic weakness of both lower extremities, more severe on the right, although the patient was able to walk with a cane. Bilateral clumsiness and tremor on the finger-to-nose test and incoordination of fine hand movements were observed. The reflexes were hyperactive throughout, with sustained clonus at both ankles. Babinski and Hoffmann signs were present bilaterally, and the superficial abdominal reflexes were absent throughout. There was slight impairment of vibratory sense over the lower part of the right lower extremity.

The spinal fluid was under normal pressure and dynamics and was clear. It contained two lymphocytes per cu. mm., and the protein content was 86 mg. per 100 cc.; there was positive reaction to a Pandy test but complement fixation was negative. The gold curve was 1111000000. No abnormalities were noted in a hemogram, on urinalysis, or in a myelogram made shortly after admission.

Histamine was given intravenously three times weekly for ten weeks. During hospitalization the weakness of the lower extremities increased steadily. There were no acute exacerbations of any symptoms, but the patient slowly lost the ability to walk even with crutches and at the time of discharge required a wheelchair to move about. Principally because of this crippling the disability rating rose from 106 on admission to 156 at discharge in July.

This case illustrates progression of disease, unaffected by histamine treatment, during hospitalization.

*As recorded by the standard method of grading.

DISCUSSION

In cases of multiple sclerosis with a history of recent exacerbation there is generally a high percentage of improvement but, as a comparison of the treated cases with control cases indicates, this remains true regardless of histamine therapy. It is generally accepted that a variable but definite proportion of the disability following acute exacerbation can be ascribed to reversible disorder (edema, vasoparalysis?) and will improve in time.

Classification of cases as acute, progressive or stationary permits more accurate prediction of the outcome in each case. Certainly a much more accurate prognosis can be made for each attack if the history of the disease is ascertained by careful questioning.

By such history-taking it can be observed that the disease in some cases has a rather malignant course, growing worse almost without interruption from the onset of symptoms to early death. In these cases obviously the prognosis is poor with any known form of therapy; in four of seven progressive cases in which the authors administered histamine, deterioration was evidenced by changing neurological symptoms and overall increase of disability. In the other three of these seven cases the disease remained essentially unchanged during hospitalization. It might be concluded that histamine altered the downhill course, but the authors believe that the period of observation was too short. It has been learned that one patient died, a year after treatment, of decubitus ulcers and progression of multiple sclerosis. Another was readmitted to the hospital three months after discharge, and despite a second intensive course of histamine his condition has grown steadily worse.

In a third group of cases the disease is apparently stationary. In these the patient's condition, after a few years of remittent disease, remains unchanged for a long time and is apparently not affected by any treatment. Most of the patients in this group are older, and their general health is excellent; they are usually better adjusted mentally to their condition

and are content with symptomatic relief. No difference was noted, among patients in this category, between those treated with histamine and those studied as controls.

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THOSE OF YOU who occasionally find time to watch television no doubt have experienced a rise in blood pressure upon seeing announcers in white coats portraying physicians peddling proprietary medicines.

This matter has been brought to our attention on several occasions, and the A.M.A. House of Delegates requested that we "arrange a meeting of mutually interested parties in the radio and television industry" to do something about correcting this situation.

We have had a number of conferences with the National Association of Radio and Television Broadcasters. The NARTB was most cordial and willing to cooperate with us on this problem.

The NARTB brought to our attention the television code which states: "When dramatized advertising material involves statements by doctors, dentists, nurses or other professional people, the material should be presented by members of such profession reciting actual experience or it should be made apparent from the presentation itself that the portrayal is dramatized."

The NARTB has expressed complete willingness to cooperate with us in every possible way.

It is requested that any televised sequences you may note and feel to be in conflict with the code be reported to the Public Relations Department of the A.M.A., and we, in turn, will take the matter up with the NARTB.

—The A.M.A. Secretary's Letter

The Allergic Aspects of Multiple Sclerosis

HINTON D. JONEZ, M.D., Tacoma, Wash.

• *For the past ten years there has been an increasing acceptance of the theory that allergenic reaction is a causative factor in multiple sclerosis. In the study of a series of patients the author traced many attacks directly to allergenic insults. When the offending substances were removed, a quiescent period often ensued. The severest symptoms of multiple sclerosis were most often associated with food allergens, the moderately severe with molds and fungi and the least severe with pollens and chemical offenders.*

The earlier the diagnosis and the beginning of treatment, the better the chance of arresting the disease and preventing serious crippling conditions. In cases of longer duration where the patient has become crippled or bedridden, physical therapy with relaxing medication is of great value.

As BASIS FOR DISCUSSION of the allergic aspects of multiple sclerosis it is necessary first to establish the present day concept of allergy and to define multiple sclerosis. The allergy of von Pirquet and Schick, as described in their monograph of 1906, is far different from the ideas of today as expressed by leading allergists. The classic interpretation of protein sensitivity rather easily forecasts mold and dust insults, but hardly forecasts allergy as it is understood today. As to multiple sclerosis, this designation is unfortunately used frequently for undiagnosed neurological diseases, especially of the demyelinization types. The generally accepted principal diagnostic symptom of this disease is that of remissions and exacerbations, with involvement of more than one portion of the central nervous system.[37, 43, 44, 45, 62, 67] However, in only about 60 per cent of cases diagnosed as multiple sclerosis is this feature present. In the cases in which remissions and exacerbations occur, the first complaints[43] often seem bizarre[24] and only a few objective abnormalities are noted by careful examination. The symptoms frequently disappear spontaneously. A patient may have a number of attacks of transient numbness or paralysis before the development of definite signs of organic disease of the brain or spinal cord.[10, 12, 14, 15, 16, 21]

ETIOLOGIC THEORIES

There are a number of etiologic theories[35] as to the cause of multiple sclerosis, among them being vitamin or mineral deficiencies, viral infections,[38, 50] emotional instability and glandular disturbances. Applying the yardstick of remissions as being needed definitely to establish the diagnosis, most of these etiological theories can be ruled out. It is hard to visualize any of these causes striking at intervals and leaving the patient apparently normal between exacerbations, with remissions lasting up to 20 years. Kennedy,[39, 40, 41] in 1936, directed attention to allergy as a possible basis in the etiologic delineation of multiple sclerosis. He stated: "Its episodes, its remissions, the curability of its most acute crisis, its attack on the optic nerves, its neglect of sensory paths—all these things greatly resemble the happenings of localized allergic edemas after the central nervous system has come under fire. Further, the recent plaques in the rare autopsies of acute cases are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels."

That same year Putnam[46] pointed to the essential similarity between encephalomyelitis and multiple sclerosis. In 1941 he expressed the view that the origin of encephalomyelitis is in some sense an allergic reaction, adding that "it seems not unreasonable to suppose that an instability of the clotting mechanism of the blood might be one aspect of allergy."[47]

Ferraro[20] introduced the concept that demyelinating diseases, especially of the acute form, are the expression of a cerebral allergic reaction. He based his contention on the fact that in these conditions the fundamental histologic features of cerebral allergy are present.

DIAGNOSIS

Before a definite diagnosis of multiple sclerosis is made, at least five of the cardinal symptoms of this disease should be present. These symptoms should also involve more than one part of the central nervous system. The cardinal symptoms are:

1. Nystagmus.
2. Pallor of the temporal halves of the optic disks.
3. Diplopia.

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The author, who was Medical Director of the Multiple Sclerosis Clinic, St. Joseph Hospital, Tacoma, Wash., died October 11, 1953.

4. Ocular palsies.
5. Speech disturbance.
6. Ataxic tremor of the upper extremities.
7. Past pointing.
8. Loss of abdominal reflexes.
9. Increase of tendon reflexes.
10. Spasticity of one or both upper or lower extremities.
11. Urinary incontinence.
12. Spastic, ataxic or spastic-ataxic gait and station.
13. Babinski's sign.
14. Remissions leading to disappearance of part or all of the symptoms.

Multiple sclerosis is a disease of adult life, initial attacks occurring usually between 20 and 40 years of age; rarely after 45 and seldom before 15 years.

At the Multiple Sclerosis Clinic, St. Joseph's Hospital, Tacoma, the histories of 2,000 consecutive cases of multiple sclerosis, definitely diagnosed by accredited neurologists or by physicians at well-known general clinics, were reviewed and, on the basis of symptoms, classified in various categories. (Table 1).

For the purposes of this presentation the 1,199 cases (Table 1) in which there was history of complete remissions and the involvement of more than one part of the central nervous system, can be designated as cases to which the theory of allergic cause can be applied. It is to be noted that only about 60 per cent of the 2,000 cases satisfied these requirements. It is quite possible that in others the initial attack may be so severe and so damaging as to prevent the patient from ever becoming symptom-free again.

TABLE 1.—*Classification, after review of records, of 2,000 consecutive cases previously diagnosed*

	No. cases	Per cent
Typical multiple sclerosis with remissions	1,199	59.9
Typical multiple sclerosis without remissions	349	17.5
Familial and atypical	100	5.0
Hereditary ataxia	48	2.4
Amyotrophic lateral sclerosis	51	2.6
Primary and posterior lateral sclerosis	233	11.6
Others	20	1.0
Total	2,000	100.0

THEORY AS TO PATHOLOGIC CHANGES

To understand the major role of allergy in multiple sclerosis, one must have knowledge of the pathologic changes that occur in acute and subacute cases. They can be considered analogous to urticarial wheals, scattered at various times,[29,49,55,58] throughout the entire central nervous system. The skin and the central nervous system originate from the same embryological layer, namely the ectoderm.[34] Because of this, it is reasonable to assume that the entire central nervous system might be susceptible to the same allergic insults that the skin is. When urticarial wheals occur on the skin or along the intestinal tract, there is no serious damage, as there is no pressure exerted. However, in a bony cavity such as the skull or vertebral column there is little room for expansion. Therefore, through pressure the blood supply to certain areas is obliterated; and if this pressure continues long enough,[56] the destruction of tissue in these areas occurs with resulting scar or sclerotic plaques. If the urticarial wheals disappear and the pressure is removed soon enough, the symptoms that have resulted from pressure disappear: a remission occurs. If pressure continues, a demyelinizing effect results, with irreversible changes.

For the last ten years there has been an increasing acceptance of the theory that allergenic reaction is a causative factor in multiple sclerosis; and no research project can be complete that does not take this into consideration. Rowe[51,52,53] has many times called attention to the manifestations of neurological allergic disease, stating that in his opinion foods are the worst offenders. The author has used Rowe's elimination diets for many patients with multiple sclerosis, especially those with extreme sensitivity to foods. The results have been very good in many cases.

EOSINOPHIL DETERMINATIONS

In considering the theory of allergenic cause of multiple sclerosis, the question of eosinophil content in the blood arises. Before the advent of the chamber method of counting eosinophils, the author carried on a rather elaborate set of studies of eosinophil content in multiple sclerosis. In a period of two years, eosinophil determinations were made on 5,164 specimens of blood from 271 patients with multiple sclerosis, including 116 just beginning the treatment described in later paragraphs. In these studies it was observed that (1) as formerly reported by other investigators,[9] eosinophil averages in multiple sclerosis are usually normal; (2) under treatment with histamine by any method, eosinophil content typically increases, usually reaching a maximum between the first and third months (range 0 to 29 per cent; average 5.2 per cent); (3) when determined monthly over a year of histamine therapy the eosinophil content was usually within normal range but almost always there was one fluctuation or more to a higher level.

The development of the chamber method of counting eosinophils antiquated older techniques for quantitative work, and the differential count studies were discontinued. In one series of 203 cases, determination of eosinophil content by the modified Randolph technique was carried out at the beginning and end of a two-month standard course of treatment. In this series the average proportion of eosinophils before treatment was 1.58 per cent with a range of 0 to 10.6 per cent. After treatment with histamine for two months the average was 5.52 per cent with a

range of 0 to 17 per cent. Medians for both were almost identical with the averages.

Some question is raised as to the concept of allergic disease as a histamine imbalance of the body that occurs during the state of hypersensitivity. However, the eosinophil continues to be the most baffling of all blood components. There is the factor of temporary storage from the circulation and the factors of production and loss. In the study described above most of the patients were in a state of fair remission when the determinations were made. Where there were increases, they could not be definitely correlated with exacerbations. But where there were temporary increases of the eosinophils, there appeared to be in some cases a connecting link. The content of eosinophils, however, might also be influenced by the rate with which they passed out of the blood stream into the areas of shock tissue.[11, 61]

SCRATCH TESTS

In dermal scratch tests of over 2,200 patients with demyelinating diseases, almost all were noted to be sensitive to some group of allergens, such as foods, molds, epidermal material or pollens. The author uses the scratch test as a gauge in the study of the allergenic background of patients with multiple sclerosis—taking into account the probability that as sensitized persons they may exhibit the allergic phenomena only when they are "triggered" by emotional factors.[7, 18, 48, 60, 65, 66]

EMOTIONAL FACTORS

It is well known that in the majority of patients with multiple sclerosis there are indications of emotional instability. The author is of the opinion that most have neuroses.[42] This resolves itself into the chicken-or-the-egg proposition. Does the neurosis occur first, or do the symptoms of multiple sclerosis come first? That is a question very difficult to answer, as it is hard to state definitely where subjective symptoms of multiple sclerosis begin and neurosis stops. At any rate, after carefully analyzing the cases, the author believes that any allergic insult, including instances in which emotional upset is a factor, can trigger the initial attack. There is no doubt that a great many patients have their first exacerbation as the result of trauma, accidents,[23] fright, worry, great joy, emotional upset or other stress—just as angioneurotic edema will occur as the result of any of these.

In treatment, emotional factors should be gone into thoroughly and rationally with the patients, with explanation to them of the degree to which their emotional upsets influenced the course of the disease.

Once urticarial whealing within the central nervous system occurs, whatever the allergenic factor, recurrences may be brought about by any other kind of allergic insult as well as the original one.

Relation of Severity of Disease to Specific Allergens

In correlating results of scratch tests with the multiple sclerotic condition of the patient, it was noted that the vast majority of patients who had particularly severe symptoms of multiple sclerosis had strong sensitivity to foods; those with less severe disease reacted strongly to molds and fungi; those who were least disabled had strong sensitivity to pollens, and in many instances of patients in this latter category it was noted that the episodes of exacerbations were related to the seasons when the pollens to which they were sensitive were afloat.

It is easy to see why patients sensitive to food had the severest cases of multiple sclerosis: They were exposed daily the year round to offending items. Two patients who were strongly sensitive to orange had minor but definite exacerbations whenever oranges were peeled in the same room they were in. There are many reports in the literature both from allergists and neurologists of cases in which persons sensitive to various foods had pronounced neurological symptoms whenever they ate or handled any of them.[32, 51, 52, 53] Many of the patients observed by the author complained of increased nystagmus, spasticity and many other symptoms of multiple sclerosis following the ingestion of certain foods.

It has been noted for years that there seem to be geographic factors in multiple sclerosis: The disease is much more prevalent in the northern parts of Europe and North America than in the southern parts of these continents.[31, 54] The same is true of the regions of Australia and New Zealand farthest from the equator. The disease is practically unknown in southern Asia and in the semitropical and tropical parts of the world. The places of greatest prevalence are those in which milk and cereal products such as wheat and rye—outstanding among allergens—form a high proportion of the food intake.

Swank[59] made a study of the diets of the various peoples of Europe before, during and after World War II with reference to multiple sclerosis. His conclusions were that the highest incidence of new cases of multiple sclerosis was in those countries where the largest amounts of milk and butter were used. Although he attributed the phenomenon to the relatively high consumption of animal fat, the correlation might be better explained on a basis of milk as an allergenic offender.

Ehrentheil, Schulman and Alexander,[20] working at the Boston State Hospital Multiple Sclerosis Research Clinic, reported on 65 cases in which an intensive study of sensitivity to foods was made. They

noted that rye, wheat, oats and orange juice were the worst offenders. (This corresponds with the results of the author's studies, except that chocolate, eggs and milk were found to be greater offenders than orange juice.)

In summarizing the Boston Clinic's study, Ehrentheil and co-workers stated:

"1. Ophthalmic tests with 25 different food proteins in patients suffering from multiple sclerosis showed a very high percentage of positive reactions to rye and wheat. This finding proved statistically to be significantly higher than in the random population.

"2. Allergen-free diets based on a carefully taken allergic history and on the results of ophthalmic tests brought about favorable therapeutic results in 31 per cent of the cases.

"3. In 12 cases the temporary reintroduction of the previously omitted food resulted in temporary exacerbations of symptoms."

TREATMENT

The treatment administered by the author is primarily that which would be used in the general management of a patient with any allergic condition. This includes instruction as to the avoidance of offenders, the use of allergenic extracts and the administration of histamine,[8, 13, 25, 26, 27, 28] at first intravenously and then by iontophoresis,[1, 2, 3, 4, 5, 6] or repository injections.[33, 36, 64] Histamine is the most powerful dilator of intracranial vessels known.[30, 57] Therefore, it covers that need. At the same time, when given properly it is the universal hyposensitizer and the recommended treatment for acute and chronic urticaria. Acute and subacute cases of multiple sclerosis usually respond to histamine therapy. Where there are irreversible changes in the chronic cases, little can be expected from hyposensitization other than eliminating exacerbations or rendering them less severe.

In addition to antiallergic therapy, everything available that has proven efficacious in the care of patients with multiple sclerosis is used, especially physical therapy, curare, vitamins and gonadotropic hormones. For the past six years curare has been used in a repository menstruum, and in that time more than a million doses of the material have been given, most of it injected by the patients themselves in the same manner as insulin. No undesirable reaction has been observed or reported.

The author firmly believes that antiallergic management is the most effective method of dealing with multiple sclerosis, especially acute and subacute cases. A complete, harmonious understanding must exist between the patient and the physician, be he an allergist or a neurologist. The patient must be taught to watch for events of stress, offending foods and other situations that occur in connection with symptoms. When he can himself connect exacerbations with some allergenic offense that he can avoid, fear of the disease and the future subsides.

1801 South Jay Street.

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Multiple Sclerosis

Its Frequency and Distribution, with Special Reference to San Francisco

LEONARD T. KURLAND, M.D., Dr. P.H., Rochester, Minn., and
HENRY W. NEWMAN, M.D., San Francisco

• *Epidemiologic surveys of multiple sclerosis were conducted in 1949 in San Francisco, Winnipeg, Boston, New Orleans, and Denver. Reports of cases for 1939 through 1948 were obtained from record offices, hospitals and clinics, and private physicians. The basis for the observations was the group of "probable" cases among residents.*

In San Francisco these probable cases in residents numbered 415; however, in only 146 of these was the onset between 1939 and 1948. Of the 143 patients who were white, 51 were male and 92 female. The average annual incidence based on these figures was 2.1 per 100,000—1.5 for males and 2.6 for females.

Prevalence, based on probable cases in residents on January 1, 1949, was 29.7 cases per 100,000 population—21.2 for males and 38.1 for females.

Mortality was 0.7 per 100,000 population—0.9 for females and 0.6 for males.

In comparison of the findings for San Francisco with those of other cities, both the incidence and the severity of the disease appear to decrease from north to south.

AN EPIDEMIOLOGIC SURVEY of multiple sclerosis was conducted in San Francisco in 1949 as one of five sponsored by the National Multiple Sclerosis Society "to determine the extent of multiple sclerosis in the United States and Canada and to study the influence of climate and race on the distribution of the disease."

The detailed description of the method of study and the results of the surveys in the other cities (Winnipeg, Boston, New Orleans, and Denver) have been published.[1, 2]

METHOD OF STUDY

Approval of the survey was first obtained from the San Francisco County Medical Society, the local hospital association, and the deans of both medical schools in San Francisco. Office space for the survey was provided by the Stanford University Medical School, and a member of the department of neurology* supervised the local survey. Medical students from both Stanford University and the University of California were employed and trained in abstracting hospital and clinic records and in contacting physicians and reviewing their records.

Reports of cases of multiple sclerosis diagnosed or suspected and of deaths were obtained from all registered hospitals, including outpatient departments, from clinics and nursing homes, and from the local office of vital statistics for the ten-year period 1939 through 1948. In addition, physicians in private practice were requested, by letter and telephone, to provide reports on cases observed in the previous five years and to identify any patients who were known to be still alive regardless of when they were last treated. No patient was seen in person.

Each case was classified as "probable" or "possible" according to the opinion of the physician making the most recent diagnosis. "Probable" cases were those in which clinical evidence was consistent with the diagnosis while other possibilities were reasonably excluded; "possible" referred to those cases in which no single neurologic diagnosis had been established.

In each of the cities surveyed, the survey coordinator† reviewed all case reports to eliminate duplication and non-resident cases. In all the cities except San Francisco each important source of case reports was rechecked about two years after the original survey and newly diagnosed resident patients whose symptoms had started before 1949 were added to the survey. At the same time data on patients whose diagnosis or residence had not been clarified in 1949

Epidemiologist, National Institute of Neurological Diseases and Blindness, Public Health Service (Department of Health, Education, and Welfare); Medical Director, Epidemiological Project, National Multiple Sclerosis Society (Kurland); Associate Professor of Medicine (Neuropsychiatry), Stanford University School of Medicine; Director, San Francisco Multiple Sclerosis Epidemiological Research Project (Newman).

This study was supported by a grant from the National Multiple Sclerosis Society.

The directors of the survey are indebted to the physicians of San Francisco as well as to the hospitals, clinics, and nursing homes who made their records available for confidential study; to the San Francisco City and County Department of Public Health for access to death certificates, and to the group of medical students who collected the basic morbidity data.

*Newman.

†Kurland.

were reviewed with the patients' latest physicians, and many inaccuracies in the earlier reports were thereby corrected. Unfortunately, as the San Francisco County Medical Society, for some unstated reason, objected to this later case review, it was not carried out in this city. Therefore the data for San Francisco must be considered less reliable than those for the other cities, although the original case reports collected in San Francisco, on which the tabulations were based, were more complete than those in the other cities before the case review. This uncertainty as to the thoroughness of the study makes it difficult to compare the results from San Francisco with those from the other four cities.

RESULTS IN SAN FRANCISCO

Originally reports on 562 cases were submitted. Of these, 119 were excluded because of non-residence, insufficient identification, uncertainty or change of diagnosis, or other factors. Also excluded were 28 other cases because no information other than the death certificate was available.

Of the remaining 415 cases, 316 (including 55 in which the patients had died in the ten-year period) were classified as "probable" and 99 as "possible." The ratio of probable to possible cases is similar to that reported in the other cities.[2]

Rates of incidence, prevalence, and mortality are based on the probable cases only, as in the other cities. The number of cases in which the disease developed in San Francisco in the ten-year period 1939 through 1948 forms the basis for the average annual incidence rates; the number of such patients residing in the city as of January 1, 1949, is used in the determination of the prevalence ratio; the number who died in the city between 1939 and 1948 is used to determine the average annual mortality rates.

Survival to January 1, 1949, of the patients with probable cases in San Francisco is shown in Table 1. The living or dead status of about 13 per cent of the reported patients was unknown. (In the other cities this unknown group averaged about 6 per cent.) These patients were not counted in prevalence and mortality tabulations.

Incidence and Incidence Rates

Of the 316 probable cases in the San Francisco study, in 36 the patients were residing elsewhere at the time of onset of symptoms. The residence or the time of onset was unknown in an additional 21. In the remaining 259 cases, the patients were residing in San Francisco at the time of onset of symptoms, which in 113 was prior to 1939. The average annual incidence is based on the 146 patients in whom onset occurred in the years 1939 through 1948.

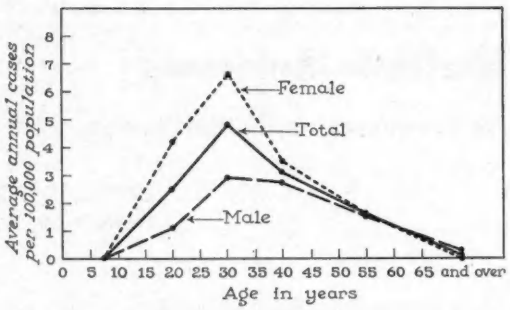

Chart 1.—Average annual incidence rates of multiple sclerosis per 100,000 population by age and sex in white population of San Francisco, 1939 through 1948.

TABLE 1.—*Distribution of patients with "probable" multiple sclerosis in San Francisco study on January 1, 1949*

Status	Number		Per cent	
Living	219		69.3	
In San Francisco		206		65.2
Elsewhere		13		4.1
Died between Jan. 1, 1939 and Jan. 1, 1949	55		17.4	
In San Francisco		45		14.3
Necropsy confirmed		7		2.2
Elsewhere		3		0.9
Status unknown	42		13.1	
Total cases	316		100.0	

Of the 146 patients, 3 were non-white—all males. Of the 143 white patients 51 were male and 92 were female. The average annual incidence per 100,000 population for the ten-year period based on these cases was 2.1—1.5 for males and 2.6 for females. The ratio of females to males was 1.7 to 1.

Chart 1 shows the average annual incidence for the white population by age and sex. A sharp peak is noted for females aged 25 through 34 years; the curve for males also reaches its maximum at this age but drops off more gradually.

The average annual incidence for nonwhites, based on the 3 cases counted and on 1950 census figures for San Francisco, was 0.4 per 100,000 population—0.7 for males.

PREVALENCE RATIOS

Prevalence of a disease in a population group is determined by dividing the number of cases by the number of persons in the group. The result, adjusted to some base number (usually 100,000), is a specific figure per unit of population and a basis for comparison among groups.

Prevalence ratios in this study were based on the probable cases of 73 white males and 133 white females reported as living in San Francisco on Janu-

ary 1, 1949. The prevalence ratio per 100,000 for the white population was 29.7—21.2 for males and 38.1 for females. The ratio of females to males was 1.8 to 1.

No probable case of multiple sclerosis, as defined for the study, was found among the 80,000 nonwhite population on January 1, 1949. It is not certain whether the study in San Francisco is as complete for nonwhites as for whites. Reports were obtained on two Chinese born in China in whom onset of disease was at ages 29 and 41 years, respectively, while they were residing in San Francisco. On one who died in San Francisco in 1948 the diagnosis was reported as confirmed by autopsy; the other was not counted in tabulations since no follow-up could be made beyond 1942. Three cases reported in Negroes were not tabulated since two were only "possible" and in the "probable" case follow-up extended only to 1945.

The nonwhite population of San Francisco in 1940 were 4,800 Negroes and 27,000 of other races, mostly Chinese. By 1950, the Negro population had increased ninefold to 43,500 and the other nonwhite groups had increased 40 per cent to 37,900, whereas the total increase in the white population was only 14 per cent.

This disproportionate increase in the San Francisco nonwhite population in the last ten years seems to be an important factor in the low rates for the group. It is likely that much of the increase in the nonwhite population is due to the migration of persons seeking employment, who would probably be in good health and because they were newer residents would not have been exposed for as long a period to any possible local disease-provoking factor as the "permanent" white population of the San Francisco area. It is also possible that differences in the medical care or reporting of cases among the large permanent Chinese population might be another factor in the difference in rates.

In Chart 2, the prevalence ratios by age for white males and white females are presented. For both sexes a peak is reached at the ages of 35 through 44 years, the age distribution curves resembling those for other cities.[2]

Deaths and Death Rates

Among white persons with probable cases, 51 died—0.7 per 100,000 population. Thirty were females (0.9 per 100,000) and 21 were males (0.6). The ratio of white females to white males was 1.5 to 1.

From 1939 through 1948, the diagnosis of 7 of the 52 probable cases for which both morbidity reports and death certificate transcripts were obtained was confirmed by necropsy. Of these 7 cases, 1 was that of the Chinese referred to previously.

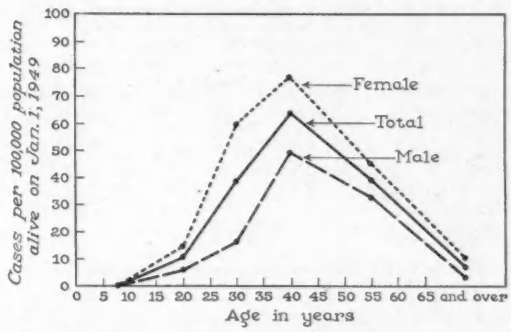

Chart 2.—Multiple sclerosis. Prevalence ratios per 100,000 population by age and sex. (Based on probable patients known to be living in San Francisco on January 1, 1949.) White population, San Francisco.

There were 28 additional deaths (15 of white males and 13 of white females) reported as due to multiple sclerosis for which no morbidity reports were submitted. Twenty-one of these deaths occurred during the period 1939 through 1944, and for most of these cases no other data were available. In some cases, the physician who reported the death was unable to supply additional information or was no longer residing in the area. It can be safely presumed that in most of the cases the onset of symptoms was prior to 1939, in which event they would have been excluded in determination of incidence rates. As the patient had died before 1949, they would not be counted in the prevalence determinations. The mortality rates alone are perhaps deficient as a result of the omission of them, but the same method was employed in the other cities in the survey and comparison of rates with the other cities is, for the most part, unaffected.

COMPARISON AND CONCLUSIONS

Comparison of results in the cities studied in the survey may permit conclusions regarding the findings in San Francisco.

1. The incidence rates for 1939 through 1948 in Boston, Winnipeg, and Denver were about three times as high as in New Orleans. The value for San Francisco was similar to that for the more northern cities (Table 2).

2. Prevalence ratios were also about three times as high in Boston, Winnipeg, and Denver as in New Orleans. The value for San Francisco was somewhat lower than for Boston, Winnipeg, and Denver, but still more than twice that for New Orleans (Table 2). The nonwhite prevalence ratio was also relatively high in Boston and low in New Orleans. In both Denver and San Francisco, the nonwhite prevalence ratio was lower than the value for whites, but in both cities the nonwhite population was relatively small

TABLE 2.—Comparison of rates of incidence, death and prevalence of multiple sclerosis in five cities (all rates per 100,000 population)

Community	Average Annual Incidence Rates, 1939-1948	Average Annual Death Rates, 1939-1948	Prevalence Ratios, January 1, 1949
Boston	2.6	1.1	41.3
Winnipeg	2.2	0.9	41.8
Denver	2.3	....*	38.2
San Francisco	2.1	0.7	29.7
New Orleans	0.8	0.2	12.9

*See text.

and had increased many times more rapidly in the last decade than had the white population.

3. The mortality rates from 1939 through 1948 in Boston and Winnipeg were four to five times as high as in New Orleans, and in San Francisco three times as great as in New Orleans. In Denver, where the mortality data were found to be deficient,[2] the mortality rate was only twice as high as that of New Orleans.

4. In all but one instance, the rates and ratios in each city were higher for females than for males. The possible reason for this difference is discussed elsewhere.[1]

5. In all cities, except New Orleans, reports of some cases of multiple sclerosis were confirmed by autopsy. (These included one report on a Chinese in San Francisco and one on a Negro in Boston.)

From these findings it can be concluded that multiple sclerosis is much less prevalent in New Orleans than in the other cities, and that the disease occurs in all races.

6. In a study of mortality due to multiple sclerosis in 1947, the death rate was found to be two to three times higher in Canada and the northern United States than in the South;[1, 3] it has been postulated that this difference in frequency with geographic latitude is somehow associated with climate. It is unknown, however, whether the frequency of multiple sclerosis diminishes gradually from north to south on this hemisphere or whether at some critical latitude or isotherm the incidence drops sharply, as it might in the absence of an important causative factor of the disease. It was hoped that the results in San Francisco might indicate whether or not there is a gradual diminution in the rates with latitude, for such information might clarify the nature of this unknown geographic factor.

Several points must be considered for further interpretation of the findings here summarized.

The rates reported in Table 2 cannot be considered as absolute measures of the frequency of multiple sclerosis but are mainly of value in comparing the relative frequency in the different cities. It is not easy to interpret mass statistics of a disease which is rare and at best difficult to diagnose, especially when the compilation of such statistics may be subject to differences in hospital record systems, in the cooperation of physicians in different communities, and in the completeness of reports on cases and deaths. By selecting large medical centers, these factors can be equalized to some extent; special studies on the completeness of the data indicate that the surveys, at least in Boston, Winnipeg, and New Orleans, were equally thorough. On recent clinical review of the cases in Winnipeg and New Orleans good correlation was obtained with the prevalence results reported here for Winnipeg, whereas in New Orleans the prevalence was found to be even less than reported in this presentation.[4]

The computation of rates and ratios depends not only on the number of cases in the numerator but also on the population base in the denominator. The greater rate of growth of the more western communities is another, although presumably minor, influence.

Further, there is greater uncertainty regarding the relative accuracy of the rates for San Francisco than for other cities in which the case review was carried out. The effect of the case review on the rates depends on whether the number of new cases discovered exceeds the number excluded because of errors in diagnosis and in reported residence. Experience in the other cities indicated that the case review did not greatly alter the total rates and ratios, but the effect on rates for subgroups separated by age and sex was in some instances appreciable.

With these qualifications in mind, the following interpretations may be made of the rates of prevalence, mortality, and incidence of multiple sclerosis in San Francisco in relation to those in the other cities:

1. *Prevalence:* The value for San Francisco was somewhat lower than the high values for the northern communities but still more than twice that for New Orleans (Table 2). Since prevalence is based on the number of cases in a city on a particular date, without regard to the residence at time of onset of symptoms, an important factor which may influence this ratio is the relative immigration and emigration of patients in the total population. So far as is known, San Francisco has not been recommended for any particular therapeutic benefit for patients with multiple sclerosis; nor is any other factor known which might cause the migration rate of persons with the disease to differ from that of the rest of the population. Taken at its face value, the prevalence ratio for San Francisco would suggest that there is a gradual decrease from north to south in the frequency of multiple sclerosis.

2. *Mortality:* As the average duration of disease

before death is 20 years, it is difficult, in a city which has increased in population so rapidly as San Francisco, to deduce reliably any short-term trends. Under these conditions, for instance, mortality rates, which are based on the number of patients dying in a recent period divided by the total population, would be very low unless the immigration of persons with advanced multiple sclerosis were in proportion to that of the general population.

3. *Incidence:* The comparison of incidence rates is probably the best measure of relative endemicity of a disease since it is computed by dividing the locally occurring cases from a recent period of years only by the current population figures. On this basis it would appear that multiple sclerosis is about equally endemic in Boston, Winnipeg, Denver, and San Francisco (Table 2). Such a finding suggests that the "northern" causative factor which seems to be absent from New Orleans may be present in San Francisco as in Denver.

It must be concluded, then, that either the method of study was not sufficiently sensitive to indicate small (but perhaps important) differences in the frequency of multiple sclerosis in San Francisco and the more northern cities studied, or that there is no appreciable difference. It does appear, however, that multiple sclerosis is a considerably greater neurologic problem in San Francisco than in New Orleans. The cause of this difference is not known.

Mayo Clinic.

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Investigation of Non-Service-Connected Cases

UNDER A NEW PLAN about to be put into effect by Veterans Administration, the Department of Justice will be called in to handle cases of suspected fraud concerning the "inability to pay" declaration of veterans with non-service connected disabilities. VA itself is forbidden by law to look behind the veteran's statement that he can't afford private treatment. According to testimony introduced in congressional hearings, this has resulted in many abuses.

The new arrangement provides that if a VA hospital manager has good grounds to suspect that the veteran's claim of indigency is fraudulent, he will confer with federal law enforcement officials. An investigation will then be conducted by the Justice Department, the regular law enforcement arm of the federal government. If the facts justify prosecution, the case will be taken to federal court. There the government will have to prove that the veteran in question set out "premeditatedly, purposefully and intentionally" to defraud the government.

Also nearing the announcement stage is a tightening up of the questionnaire filled out by veterans with non-service connected conditions when they apply for VA hospitalization. VA medical and legal officials have been working on the new wording since last spring.

It is expected the revised form will call on the veteran to supply more information about his finances.

—A.M.A. Washington Letter

The Importance of Potassium After Operation

GEORGE C. HENEGAR, M.D., Oakland

• *A deficiency of potassium in a patient after operation is manifest clinically by anorexia, malaise, apathy, weakness, abdominal distention and hypochloremia.*

Many patients who have had a prolonged disturbance in nutrition may have a "subclinical" hypopotassemia.

Prophylaxis by means of replacement of the potassium excreted daily in the urine is the ideal treatment.

When the clinical picture of potassium deficit develops, the amount of the potassium ion needed for replacement should be calculated on the basis of the total amount of water in the body of the patient.

BENEDICT,[1] IN 1915, observed a change in the urinary excretion of potassium in the state of starvation but the significance of the phenomenon was not appreciated until Darrow and Gamble[3-8, 14] began reporting upon studies of electrolyte balance. Gradually an understanding of the role of potassium in health and disease evolved and today surgeons are keenly aware of the complications that result from deficiency or excess of this ion.[2,10,11,12,13,14,15,17,20,21]

To better understand the clinical problems involved in deficiency or excess of potassium in the body, certain fundamentals must be made clear. Potassium is present in both intracellular and extracellular fluid. The quantity in intracellular fluid normally is 115 milliequivalents per liter, and in extracellular fluid approximately 5 milliequivalents per liter. Therefore, although a change in the amount of potassium in the serum is of some significance, it is only a rough estimate of what changes are occurring within the cells. In ordinary circumstances there is a constant excretion of 60 to 90 milliequivalents of potassium in the urine and 10 milliequivalents in the feces per day. This remains fairly constant in spite of the intake except when the body is greatly depleted. At such times, the urinary and fecal excretion is lowered only slightly.

In the course of 24 hours the average adult secretes approximately 8,200 cc. of fluids into the digestive tract. This greatly exceeds the total volume of plasma (some 3,500 cc.) but a state of equilibrium is maintained by the reabsorption of much of this fluid. The amounts of the various digestive secretions entering the digestive tract of an adult human are shown in Table 1.[14] The ionic loss of these secretions is shown in Table 2. In a healthy person there is no actual loss from the gastrointestinal tract other than the fecal excretion of 10 milliequivalents of potassium per day. However, in patients with intubation, vomiting, diarrhea or intestinal fistula, the intestinal fluid loss becomes significant: Both water and electrolytes are lost. If, in the replacement of the total fluid loss, only dextrose in water and/or saline solution is given and no attempt is made to replace the potassium, a pronounced drop in the serum potassium level with the characteristic clinical features will result. This may be overlooked if serum potassium determination is carried out during the dehydrated state and the content is found to be "normal." Not until the amount of extracellular fluid is returned to near normal will there be an appreciable decrease in the potassium content of the serum.

This brings up the question of total body water and its various partitions. Recent studies[9, 18] have shown that the muscle mass as compared to the fat mass plays a very important role in determination of total body water. Lean persons have relatively more water in the body than do obese persons. Another

TABLE 1.—*Total volume of digestive secretions produced in 24 hours by adults of average size*[14]

Saliva	1,500 cc.
Gastric secretion	2,500 cc.
Bile	500 cc.
Pancreatic juice	700 cc.
Intestinal secretion	3,000 cc.
Total	8,200 cc.
Blood plasma volume	3,500 cc.

TABLE 2.—*Average gastrointestinal tract losses expressed in milliequivalents per liter*[21]

	Sodium	Potassium	Chlorides
Gastric secretion	59.0	9.3	89.0
Small bowel secretion (Miller-Abbott suction)	104.9	5.1	98.9
Ileum secretion (Miller-Abbott suction)	116.7	5.0	105.8
Ileostomy (recent)	129.5	16.2	109.7
Cecostomy	79.6	20.6	18.2

Part of a Symposium on Nutrition and Electrolytes presented before the Section on General Surgery at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24-28, 1953.

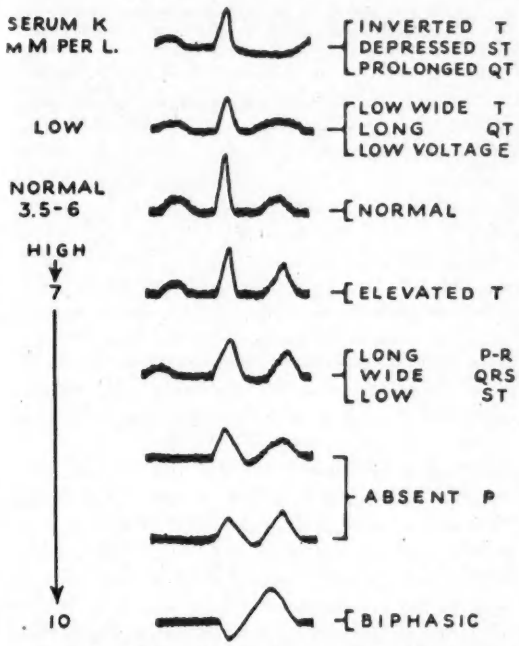

Figure 1.—Changes in the electrocardiographic tracings produced by alterations in serum levels of potassium. Darrow, D. C., and Pratt, E. L.[8]

point to be kept in mind is the change in per cent of body water produced by fat loss in the patient who has lost weight due to illness or secondary to catabolism of fat in trauma or surgical operation. These points are brought up to emphasize the need for a knowledge of total body composition before the electrolyte needs can be calculated with any reasonable accuracy.

The electrocardiographic changes produced by hypopotassemia frequently are characteristic (Figure 1). Moderate potassium deficiency is associated with a low, wide T wave with prolonged QT and low voltage in all the leads. As the potassium is further depleted the T wave is inverted, ST depressed and QT further prolonged. On the other hand, elevation of the potassium above normal causes an elevated T wave with progression to a biphasic pattern as the potassium reaches toxic and lethal levels. Electrocardiographic tracings are less helpful in cases of mild to moderate aberration of potassium levels unless a base line is established with preoperative tracings. This is particularly true when operation is done on older patients in whom some unrelated electrocardiographic variation from normal may already exist.

CLINICAL FEATURES OF HYPOPOTASSEMIA

Before the present understanding of hypopotassemia many patients had serious postoperative complications owing to the condition and some even died in a state so aptly termed "la maladie post-opératoire" by Leriche.[16] Postoperative apathy, lethargy, anorexia, weakness, abdominal distention and hypochloremia are characteristic symptoms. Time was when such symptoms, particularly after operations on the gastrointestinal tract, often led to reoperation on the assumption that there was intestinal obstruction, which only aggravated the electrolyte problem.

The following case illustrates the problems of diagnosis and treatment of hypopotassemia:

REPORT OF A CASE

A 61-year-old Chinese male was admitted to the hospital on September 27, 1952, with a history of "indigestion" of ten years' duration and diabetes of eight years' duration. Before he was admitted, active duodenal ulcer with considerable obstruction was diagnosed. It had not been relieved by conservative treatment.

Nasogastric suction was started soon after the patient was admitted and 2,000 cc. of gastric fluid was aspirated in the first twelve hours. A modified Sippy regimen was prescribed and aspiration to remove gastric residue was carried out daily.

On October 1, 1952, the content of chlorides in the serum was down to 85 milliequivalents per liter and the carbon dioxide content up to 32 milliequivalents per liter. The alkalosis was considered to be due to the loss of chlorides in the aspirated gastric juice and it was corrected by intravenous infusion of ammonium chloride solution.

Vagotomy and gastroenterostomy were done October 3, 1952. This operation rather than subtotal gastric resection was decided upon because the duodenum was densely adherent to the inferior surface of the liver in the region of the extrahepatic biliary tree. An hour after operation the sugar content of the blood (fasting) was 204 mg. per 100 cc.

Convalescence was uneventful until on the tenth postoperative day the patient began to vomit. Approximately three liters of fluid was vomited in 12 hours. The following morning it was noted that the output of urine for the preceding 24 hours had been only 250 cc. Clinically the patient did not appear to be dehydrated. The abdomen was soft and non-tender and peristaltic activity was normal. Obstruction secondary to an edematous gastroenterostomy stoma was considered likely. Therefore not all the fluid lost was replaced.

The patient was given, by vein, 1,000 cc. of 5 per cent Aminosol,® 1,000 cc. of 5 per cent dextrose in 0.45 per cent saline solution, to which one 10 cc. ampule solution of "K-M-C,"* one 2 cc. ampule vitamins (Berocca®) and 10 units of regular insulin were added. This supplied a total of 77 milliequivalents of sodium, 25 milliequivalents of potassium, 10 milliequivalents each of calcium and magnesium and 102 milliequivalents of chloride ions. After the infusion the total protein content of the blood was 7.66 gm. per 100 cc., of which 4.32 gm. was albumin and 3.34 gm. was globulin.

On the following day, October 15, the patient appeared to be severely dehydrated. He was weak and singultus had developed. In the preceding 24 hours the total intake of fluids was 2,340 cc. with the output 3,070 cc. Of the output,

*"K-M-C," a solution prepared by the Ingram Laboratories, San Francisco, contains 25 milliequivalents of potassium, 10 milliequivalents of magnesium, and 10 milliequivalents of calcium in 10 cc. distilled water.

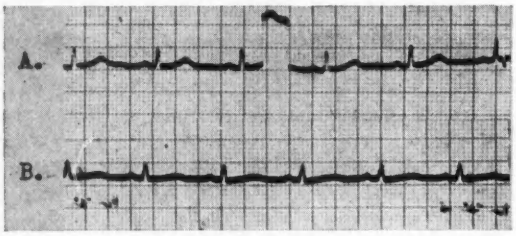

Figure 2.—Case 1, Electrocardiographic tracings: *A.* Preoperatively on June 6, 1952. *B.* Tracing made on Oct. 16, 1952 showing a low T wave with a prolonged Q T interval.

100 cc. was urine, 2,170 cc. was withdrawn by nasogastric suction and 800 cc. was calculated as insensible loss.

The content of electrolytes in the serum on that day was as follows: Potassium 5 milliequivalents, chlorides 100 milliequivalents, carbon dioxide 46.3 milliequivalents (see Table 3). The patient was alkalotic and dehydrated, but because the potassium content in the serum was normal, only 50 milliequivalents of potassium was added to the parenteral fluid for that day. The total fluid intake was 4,830 cc., of which 500 cc. was whole blood, while the fluid output approximated 2,550 cc., of which 850 cc. was urine and 900 cc. was gastric aspirate.

Next day the patient appeared semi-comatose and had "fish mouth respirations." A metabolic disturbance secondary to diabetes mellitus was considered but this seemed unlikely. Although the sugar content of the blood was 417 mg. per 100 cc., alkalosis was present and potassium deficiency seemed the most probable cause. This diagnosis was supported by comparison of T waves in an electrocardiogram taken at that time with the T waves in a tracing made preoperatively (Figure 2).

It was learned that the patient had not received all the fluids ordered for him in the preceding 24 hours. The total intake was 3,180 cc. and the output 1,410 cc. of urine, 730 cc. of gastric aspirate and 800 cc. of insensible fluid loss. Therefore, 75 milliequivalents of potassium, well diluted, was given slowly by vein.

On October 17 the patient was still dehydrated and thirsty but no longer semicomatose. The body weight was 109 pounds. There appeared to be very little fat in the subcutaneous tissues. Ninety-five milliequivalents of potassium in four liters of fluid was ordered for the next 24-hour period.

Next day the patient was considerably improved. The gastric residue was 500 cc. Mineral oil was given orally to see if it would pass through the stoma. The potassium content of the serum was 3.55 milliequivalents, of chlorides 90.1 milliequivalents, and of carbon dioxide 48 milliequivalents. The potassium deficit was approximately 1.5 milliequivalents per liter. An infusion of 110 milliequivalents of potassium in 3 liters of fluids was given.

On October 19 the oil passed through the gastrointestinal tract. The patient began to take a soft diet. In addition to the oral intake, 105 milliequivalents of potassium in 3 liters of fluids was given by vein.

Next day the patient felt well and the content of electrolytes in the serum was nearly normal. The body weight was 118½ pounds. Two days later the patient was discharged from the hospital.

TABLE 3.—*Summary of blood chemical determinations in milliequivalents per liter in case herein reported*

Date	Sodium	Potassium	Chlorides	Carbon Dioxide	Potassium Therapy (mEq.)
October 1	.....	.....	85.0	32.0	.....
October 2	143	.....	.....	.....	.....
October 6	.....	.....	93.2	31.4	.....
October 15	.....	5.0	100.0	46.3	50
October 16	.....	.....	.....	.....	75
October 17	.....	3.05	90.1	48.0	95
October 18	.....	3.55	90.1	37.5	110
October 19	.....	.....	.....	.....	105
October 20	.....	4.4	109.0	25.0	.....

DISCUSSION

Several features that are common in postoperative metabolic problems were present in the case here reported. The patient had nutritional inadequacy of long standing due to an obstructing lesion in the duodenum. This led to "subclinical" intracellular potassium deficiency which was probably secondary to low content of protein in the cells.

If postoperative convalescence had not been complicated by the loss of a large amount of fluid and electrolytes through vomiting, the potassium deficiency might have been corrected spontaneously. Owing to the loss of fluid and the dehydration of the patient, the potassium deficiency was not detected when the serum content was determined the following day. It became apparent, however, in determinations carried out after fluids had been infused to replace the fluids lost, and the patient lapsed into a state typical of hypopotassemia, characterized by semicoma, anorexia, abdominal distention and extreme weakness. The potassium deficiency was not as great as might have been expected in light of the serious clinical condition of the patient. The potassium depression was 1.95 mEq. per liter. With the lowered body weight (109 pounds), the total deficit was only 58.5 mEq. Although approximately that amount was replaced in the three days after deficiency occurred, the amount of potassium which was being excreted in the urine daily was not taken into account. Urinary output was so low that there was a tendency toward over-caution against supplying too much potassium. This proved to be in error. It was not until enough potassium to replace that excreted, as well as to make up the deficit in the serum, was supplied that the patient recovered. Although the electrocardiogram taken at the time of potassium deficiency was of some value in diagnosis, it probably would not have been had there been no preoperative tracing to compare it with. By itself the tracing shows very little that might be considered characteristic of potassium deficiency.

Avoiding pathologically low potassium is usually no problem if the patient can begin adequate oral intake within the first three to five days postoperatively. In some cases, such as the one cited, the patient may have unrecognized low potassium that may

not be manifest even on serum potassium studies. If kidney function is good, patients may safely receive 60 to 90 mEq. of potassium daily in parenteral fluids until such time as they may take adequate fluid or food by mouth.

If considerable potassium deficit develops, replacement must be governed by the degree of deficit. Since the potassium ion is so distributed in the body that it exists in the intracellular fluid in a much higher concentration than in the extracellular fluid, replacement should be considered on the basis of total body water. For example, a deficit in the serum of 2 mEq. per liter, in a patient with body weight of 50 kilograms would be replaced in the following fashion: If the patient is lean, body water may be assumed to make up 60 per cent of the body weight, or 30 liters. The deficit of 2 mEq. per liter, times 30 liters, equals 60 mEq. of potassium ion needed to overcome the deficit. If the daily excretion of potassium is another 60 mEq., then the patient should receive 120 mEq. of potassium in a 24-hour period. Potassium should be administered slowly in divided doses lest hyperpotassemia develop.

Adequate renal function is, of course, necessary. It must be kept in mind that the response to replacement of potassium ion is often slow; potassium administration may have no observable effect clinically or on the potassium content of the serum for 48 hours following therapy.

Potassium solutions used in prophylaxis and replacement are numerous. Where laboratory facilities are limited, the prepared solutions* such as one which Fox[13] described may be used to replace part of the fluid and electrolyte requirements.

The prepared solutions, however, often contain too much of an ion that may not be needed in the circumstances—sodium in the first few postoperative days, for example. The ideal replacement is by means of addition of the required ions. Potassium chloride solutions are available in which 1 gm. is equal to approximately 13.3 mEq. of potassium ion, when diluted to 1 liter. These solutions can be added to any other solution given by vein. Two gm. of potassium chloride added to each liter of fluid given will give enough of the potassium ion to replace that lost in the daily urinary excretion.

3400 Webster Street.

*Polysal® (Cutter) contains sodium 140 mEq., chloride 103 mEq., bicarbonate 55 mEq., potassium 10 mEq., calcium 5 mEq., and magnesium 3 mEq. per liter.

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Tuberculosis Control in California Mental Hospitals

E. H. CRAWFIS, M.D., Sacramento, EDWARD KUPKA, M.D., Berkeley, and WALDO R. OECHSLI, M.D., Los Angeles

• *Diagnosis, the first step in tuberculosis control, is accomplished in the mental hospitals of California by x-ray examination of all patients annually and of new or returning patients on admission. This routine has been carried on since 1937.*

Tuberculous patients with active disease are segregated in one of three specially staffed and equipped units at the Patton, Sonoma and Napa hospitals. Those in whom disease is likely to recur are likewise segregated for special care and observation. Those in whom disease is inactive or not definitely diagnosed are not segregated but are observed by physicians of the Bureau of Tuberculosis Control of the California Department of Public Health in collaboration with the staffs of the institutions.

Since the establishment of this program the proportion of new or previously unrecognized cases of tuberculosis has been reduced from 0.83 per cent, a year after the program was begun, to 0.37 per cent, while recurrence or progression of previously recognized disease has been reduced from 12.3 per cent at the first survey to 5 per cent at the most recent.

Overcrowding in all hospitals has been the chief obstacle to the success of the program.

PROGRAMS for the control of tuberculosis in mental institutions are not new and many states now have them. One of the first such programs was begun in the province of Ontario in 1930 and has operated annually on a well organized basis since 1937.[5] The New York Department of Health, recently reviewing ten years of experience in such a program, reported a significant decrease in the number of cases in successive surveys.[1] While there were many factors contributing to the decrease, the major ones were early diagnosis and segregation of patients.

The relatively high incidence of tuberculosis among patients with mental disease has been commented upon many times. The New York report indicated that this is true before as well as after admission to hospital. In a high proportion of cases the mental disorder is such as to predispose to poor health habits. Overcrowding in mental institutions and lack of personnel aggravate this predisposition. In these institutions, however, because of the relatively static population and because the movement and environment of patients can be controlled, an effective program of tuberculosis control may be developed.

Such a control program has two aspects. The first is diagnosing tuberculosis in its earliest stages, which is done by an initial mass survey of all patients, roentgen examination of the chest of each patient upon admittance, and annual surveys to find newly developed cases. Once such a case-finding program is begun, segregation and isolation to prevent transmission of infection to others and a treatment program for patients with active disease must follow.

The tuberculosis case-finding program of the California Department of Mental Hygiene started with preliminary fluoroscopic and x-ray surveys in 1943,[2] and continuing annual x-ray surveys of all the patients in the hospitals was begun in 1946.[3, 4] The surveys are carried out by the Bureau of Tuberculosis Control in the California Department of Public Health, using mobile x-ray units. Employees are included in the surveys if they wish to be. At the time of the first survey (1946), the institutions began the routine x-ray examination of all patients admitted or returning from absence.

The policy of centralizing tuberculous patients in special units in selected hospitals was followed from the outset. As psychotherapy must be continued, the concentration of specially trained personnel and of facilities results in better treatment for patients; it also lessens the risk of infection to other patients and employees. The most obvious disadvantage of such a policy is that some patients are hospitalized many miles from their homes with consequent inconvenience for visiting relatives. It also imposes a considerable burden of moving tuberculous patients between institutions. Patton State Hospital was designated as the special tuberculosis center for Southern California and the Napa State Hospital for Northern California. Sonoma State Home was designated as the tuberculosis center for mentally deficient patients. As a part of this program a new tuberculosis unit was opened at Patton in October 1951 and another at Sonoma (February 1951). Shortly a new unit will be built at Napa. Until it is available the tuberculous patients for the northern institutions will continue to be cared for at both Napa and DeWitt state hospitals.

TABLE 1.—*Results of first five x-ray surveys in nine mental hospitals of California.*

Survey	1946-47	1947-48	1948-49	1949-50	1950-51
No. of patients whose previous survey or hospital film was negative (new cases)	.....	124 (0.47%)	80 (0.30%)	43 (0.16%)	52 (0.18%)
No. of patients not previously x-rayed or disease not recognized previously	.....	96 (0.36%)	53 (0.20%)	61 (0.22%)	54 (0.18%)
Total No. patients with x-ray evidence of new or previously unrecognized pulmonary tuberculosis	2139 (8.25%)	220 (0.83%)	133 (0.50%)	104 (0.38%)	106 (0.37%)

Percentages refer to total patient population, which varies at each survey.

The treatment available at these centers has improved greatly in the past few years. New therapeutic methods and particularly the use of antibiotics and other new drugs have been of invaluable assistance. A beginning has been made in supplying major thoracic operations. Professional and nursing staffs have been expanded as have laboratory, x-ray and surgical facilities. The effectiveness of the program is shown in the significant decrease in the proportion of previously unsuspected cases with successive surveys[4] (Table 1).

Some patients could not be sent to the special institutions, owing to lack of facilities. X-ray examination of them was carried out at each resurvey, and a study was made with particular reference to those in whom films showed new infiltration, cavitation or definite increase in the area or density of preexisting infiltration. The presence of any of these changes was interpreted as reactivation or progression of disease. It was found in the second survey (Table 2) that one in eight (12.3 per cent) of the non-segregated patients had x-ray evidence of such a progression of disease; 2.3 per cent among these had cavitation of lesions where there had been no evidence of it previously. There was a sharp reduction in the third survey in the number of cases with progression (8.6 per cent), and further reduction to 5.0 per cent in the sixth survey, which indicated improvement in the efficiency of segregation with each survey. These findings were based upon serial x-ray examination. Although an important part of the tuberculosis control program is the laboratory confirmation of activity of tuberculous lesions by means of sputum examination, unfortunately the mental institutions have had great difficulty in getting laboratory technicians. As a result, information regarding sputum findings is too sparse to be of statistical significance. This does not detract from the significance of the data, however, since serial x-rays, if the films are technically good and are compared carefully, reveal with considerable accuracy progressive or retrogressive changes in pulmonary lesions. Progression of lesions, as shown by serial x-ray films, is considered satisfactory evidence of activity of the disease process.

TABLE 2.—*Reactivation or progression of known tuberculosis among unsegregated mentally ill patients, as observed in x-ray surveys*

Survey	Total Number of Unsegregated Patients X-rayed	Number Showing Reactivation or Extension of Disease
1947-48	261	32 (12.3%)
1948-49	221	19 (8.6%)
1949-50	370	24 (6.9%)
1950-51	410	35 (8.5%)
1951-52	516	26 (5.0%)

Early in the control program it was necessary for each institution to improvise quarters for the large number of patients with tuberculosis found in the initial survey (Table 1), on admission, and in subsequent surveys. At first most of the patients were being cared for on ordinary wards with no specialized facilities and by personnel not trained in appropriate tuberculosis techniques. During the early part of the period of the case-finding program, very few of the nine institutions had tuberculosis specialists on their staffs, either as residents or as visiting consultants. At present each hospital has a competent consultant in tuberculosis and several now have full-time tuberculosis specialists on the staff.

In addition to the problems of care and segregation, the mental hospitals were seriously overcrowded during these years. In 1946 average overcrowding in all institutions was 25 per cent; overcrowding at Napa was 36 per cent, at Patton 23 per cent, and at Sonoma 39 per cent. In 1947, by the addition of new beds, the average overcrowding was reduced to 17 per cent for mentally ill patients and to 26 per cent for the mentally deficient patients at Sonoma. By 1948 overcrowding in the state's institutions for mentally ill patients had been reduced to 15 per cent, and that condition now obtains.

Because of overcrowding, segregation was not complete, particularly in relation to several classes of patients. Patients classified as having active or probably active tuberculosis were segregated first. Less attention was given to segregation of patients with questionable activity and less still if the disease was classified as probably inactive. As a result of the findings in subsequent surveys, it was felt that reactivation of the disease in non-segregated patients with supposedly inactive disease was a significant hazard, and the Bureau of Tuberculosis Control of

the California State Department of Public Health was asked to make a survey of all cases of tuberculosis among patients in the hospitals of the Department of Mental Hygiene.

The primary reason for the study was to devise a simple and fairly dependable method of dividing patients into categories of infectiousness, probable infectiousness, and probable non-infectiousness. This meant a review of all patients in whom tuberculosis had ever been diagnosed or suspected.

Almost 3,500 sets of x-ray films of the chest in chronological order were reviewed by the medical staff of the Bureau of Tuberculosis Control in collaboration with the staff physicians of the hospitals, and with the patients' charts at hand, so that all available information could be connected. Each of the tuberculosis specialists had had long experience in institutional treatment of tuberculosis and in the interpretation of films of the chest.

In addition to the classifications and policies established through the survey, certain other notable benefits were derived:

The careful review of every case proved to be invaluable to the three consultants as well as to the resident staffs. To the consultants it gave a detailed quantitative and qualitative picture of the tuberculosis care problem in each institution which could have been obtained in no other way. To the resident staff, the critical review gave aid in making decisions on borderline cases, suggested additional diagnostic procedures, promoted the use of the standard National Tuberculosis Association diagnostic classification, and brought more patients to therapy with drugs and operation.

The review also permitted the dropping from the records of a large number of diagnosed or suspected cases which had been carried needlessly. To the harassed administrators of the dangerously overcrowded institutions, who feared intramural spread of tuberculosis, it brought help in that the patients with really dangerous tuberculosis were identified and isolated and those with reasonably safe arrested cases could be placed in non-segregated quarters.

After a pilot study at the Sonoma State Home, five categories of cases were established, and this division has been applied in the other institutions as well. The categories and the policies with regard to them are as follows:

A. *Patients in whom active disease is either demonstrated or strongly indicated.* These patients are segregated in the units already established.

B. *Patients in whom the disease is relatively inactive but is most likely to become active.* This category includes patients in whom lesions were active in the fairly recent past, or were very extensive at any time, and also recently admitted patients in whom a single film indicates tuberculosis that may become active.

As reactivation of pulmonary tuberculosis occurs almost exclusively among such persons, it was decided that patients in this category also should be sent to the hospitals with tuberculosis units, so that they could be under the care of specially trained personnel. At the present writing this has been done with all but a few in this category who are still segregated in the other hospitals. These patients, while not under active treatment, receive special care and diet and are roentgenographically examined every three months.

The segregation of these patients increased the total of segregated patients by 832. A few beds were already available in the special units for patients with active disease, but for most of the number it was necessary to set up additional wards in the three tuberculosis centers.

C. *Patients in whom recurrence of tuberculosis is less likely.* These include patients who have relatively insignificant fibrotic or fibrocalcific lesions, most of which are very small in extent, with no evidence of activity for several years. A sharply circumscribed "tuberculoma" of less than 1 cm. diameter may be considered a lesion of this category. Since the probability of reactivation of disease among such patients is much less likely, they are not segregated but have x-ray examination of the chest every six months.

TABLE 3.—*Classification of tuberculosis patients with known or suspected tuberculosis—Totals to August, 1952*

	Classification*					
	A	B	C	D	E	Total
Mentally ill	841	777	1,024	87	351	3,080
Male	572	446	638	54	220	1,930
Female	269	331	386	33	131	1,150
Mentally defective	82	55	136	23	67	363
Male	41	29	78	11	34	193
Female	41	26	58	12	33	170
Segregation indicated:						
Mentally ill	841	777	.....	....	.....	1,618
Mentally defective	82	55	.....	....	.....	137
Total	923	832				1,755
X-ray and laboratory follow-up but no segregation:						
Mentally ill	.....	.....	1,024	....	.....	1,024
Mentally defective	.....	.....	136	....	.....	136
Total			1,160			1,160
Removed from tuberculosis register:						
Mentally ill	.....	.....	.....	87	351	438
Mentally defective	.....	.....	.....	23	67	90
Total				110	418	528

*A—Probably active disease; B—Recurrence strong possibility; C—Recurrence less likely; D—Primary lesions only; E—Non-tuberculous disease.

D. *Patients with simple calcified primary lesions.* This category represents the former routine of including every case of pulmonary calcification of the Ghon type on the tuberculosis register. As such entries are no longer made, the category will disappear. No action is taken in these cases.

E. *Patients with miscellaneous non-tuberculous conditions:*

1. Those in whom pulmonary tuberculosis has been tentatively diagnosed or in whom infiltration of the lung fields has been observed, but in whom at least one thoracic film shows clear lung fields.

2. Those with infiltration of the lung which by location or progress seems symptomatic of other condition, particularly suppuration of the lung.

3. Those with other kinds of infiltration of the lung or other abnormalities which do not seem due to tuberculosis and cannot be diagnosed without further studies.

4. Those in whom thickening or calcification of the pleura of undetermined origin is observed but no parenchymal lesions are demonstrated.

Improvement of diagnostic methods should result in reduction of the number of cases in Category E. Patients so classified are not segregated.

The results of the survey and the policies here outlined were explained to the staffs of the mental hospitals at two regional meetings. The chief benefits resulting from those meetings are (1) improvement of isolation techniques for patients with active disease; (2) encouragement of a more active treatment program; (3) development of a program for the care and segregation of patients in whom disease may recur; (4) better understanding and compliance with recommendations for segregation of particular patients. Although this phase of the program has been in effect only a short time, the value of it is felt to be considerable.

Two other advantages of the control program should be noted. One is the simplification of staffing and budgeting. It is simpler, for example, to explain the drug requirements for a tuberculosis unit of 500 patients than to explain the same requirements as components of the drug budgets of five or six hospitals.

A final advantage is the fact that employees of the institutions are appreciative of the value of the program. If there is delay in transferring a patient to a tuberculosis unit after active disease has been diagnosed, employees become uneasy and call the matter to the attention of the hospital administration.

1320 K Street, Sacramento.

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Cortisone and Corticotropin (ACTH)—A Review

E. E. HARNAGEL, M.D., Los Angeles

FOUR YEARS AGO, Hench, Kendall, Slocumb and Polley[51] reported that cortisone and corticotropin (ACTH) effect pronounced and prompt improvement in the signs and symptoms of rheumatoid arthritis. The introduction of two potent agents effective against a disease for which therapeutic agents were sorely lacking was promptly hailed as a major contribution to medicine, but of perhaps greater importance was the demonstration by the investigators that cortisone and corticotropin have a physiologic property, theretofore not generally recognized—the ability to suppress or inhibit inflammatory reaction of mesenchymal tissue, occurring in a variety of diseases. The implications of this discovery have been far-reaching, extending into every field of medicine and surgery. The employment of these hormones in over one hundred disease states has been reported. In some, there apparently has been a rational basis for their use suggested by one or more of their physiologic actions. In others, trial has been purely empiric, justified perhaps by the assumption that these substances may have other physiologic effects as yet undiscovered. An enormous volume of medical literature has appeared incident to these investigations. One published bibliography lists over 3,000 articles which have appeared in less than three years and the list is still growing.[22] The purpose of this review is to select from this enormous literature only a few data on the physiologic and pharmacologic actions of these hormones which appear to be of particular significance to clinicians. For a more comprehensive summary of all adrenocortical steroids and corticotropin the recent series of articles by Thorn and his colleagues is highly recommended.[113]

NATURE OF CORTISONE AND CORTICOTROPIN

Cortisone is a steroid and, like cholesterol, sex hormones and bile acids, contains a phenanthrene nucleus (Figure 1). It was isolated from the adrenal cortex in 1935, and a definite chemical formula assigned to it in 1938 by Kendall and his co-workers.[72] According to Polley and Mason, the significant features of this compound upon which its antirheumatic (and probably anti-inflammatory) properties are dependent are the presence of a ketone group at C-3, a double bond between C-4 and C-5, either a ketone or hydroxyl group at C-11, a ketone group

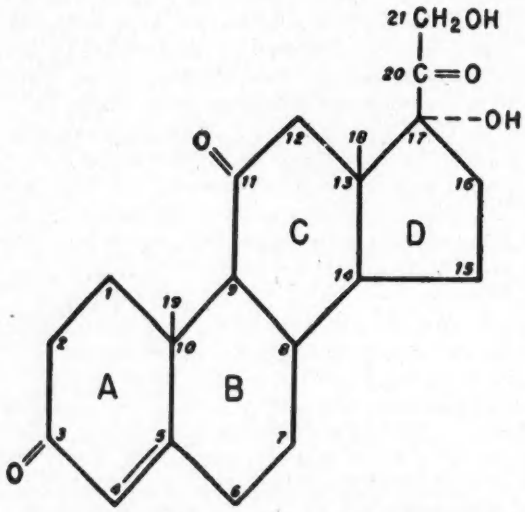

Figure 1.—Chemical formula of cortisone (11-dehydro-17-hydroxycorticosterone or Compound E of Kendall).

at C-20, and hydroxyl groups at C-17 and C-21. The only other steroid that fulfills these criteria is 17-hydroxycorticosterone, or Compound F of Kendall; and it is the only steroid of the many which have been investigated which appears to have significant antirheumatic effect.[90]

Corticotropin is a protein with a molecular weight of approximately 20,000. The hormone has not been isolated in pure form and its chemical formula is not known. Its biologic activity is destroyed by several enzymes, which suggests that one or more peptide bonds are present. It may contain such amino acids as tyrosine, tryptophane and arginine.[6] The studies of Li and Lesh suggested that corticotropic activity may reside in several peptide fractions.[66, 69]

PREPARATIONS

Cortisone is commercially prepared as an acetate ester. The biologic activity of cortisone and cortisone acetate is essentially the same. It is available in 5 mg., 10 mg. and 25 mg. tablets for oral administration, and in a liquid preparation for intramuscular or subcutaneous injection, containing 25 mg. of cortisone in each cubic centimeter. It is also available in a 1.5 per cent ointment and in 0.5 per cent and 2.5 per cent suspensions for ophthalmic use.

Corticotropin is available either as a lyophilized powder in vials containing 10, 25 or 40 provisional U.S.P. units or as a stable solution containing 40 U.S.P. units in each cubic centimeter. A long-acting preparation of lyophilized corticotropin in gelatin is available in 5 cc. vials containing 20 or 40 U.S.P. units in each cubic centimeter. In the past year, a new preparation known as purified corticotropin has become available and will in all probability replace the older long-acting preparation.[80] When administered subcutaneously or intramuscularly, purified corticotropin has a greater clinical effect, unit for unit, than has corticotropin. For convenience, however, the potency of this new preparation is expressed in terms of *clinical activity*, equivalent to a specified number of U.S.P. units of corticotropin, so that a change from corticotropin to purified corticotropin can be made without gross alterations of dose. It is available in 5 cc. vials containing 20 or 40 U.S.P. units in each cubic centimeter.

METHODS OF PREPARATION

The amount of cortisone available by extraction from adrenal glands is exceedingly small. Shortly after the hormone was isolated and its chemical formula ascertained, research began in several laboratories in an effort to produce this hormone synthetically. This was finally accomplished in 1946 by Sarett of Merck Laboratories, using desoxycholic acid derived from beef bile as a starting material.[98] Its preparation is the most complicated procedure in the pharmaceutical laboratory today. Nevertheless, in the past year production has been catching up with the tremendous demand for the hormone. This increased production and presumably competition among various manufacturers has made possible a price reduction to 5 per cent of the cost in 1949.

Corticotropin may be extracted by several methods from hog, sheep and beef pituitary.[5, 70, 99] Astwood and colleagues recently reviewed methods of extraction and purification.[6] Since the chemical formula of corticotropin is unknown, it would seem unlikely that it will ever be produced synthetically. However, there is a possibility that a peptide fraction which appears to have physiologic properties similar to the protein form may some day be synthesized.[63] Early corticotropin preparations were occasionally contaminated by minute quantities of other pituitary substances, particularly posterior pituitary fractions, but with recent advances in purification, contamination has been almost completely eliminated.[40] To humans, corticotropin derived from animal sources is a foreign protein, and sensitivity reactions, although uncommon, have been observed. Pyrogenic reactions, urticaria and contact dermatitis have been reported.[14, 52, 71, 125]

METHOD OF ASSAY

Corticotropin is assayed by an adrenal ascorbic acid depletion test devised by Sayers, Sayers and Woodbury, in comparison with a provisional U.S.P. standard.[1, 100] There is likely to be considerable variation in different batches of any substance which must be assayed by biologic methods. According to Mote, a statistical variation of less than 20 per cent in the Sayers and Sayers bioassay technique is considered good; variations of a greater magnitude are not uncommon.[77] Furthermore, all brands of corticotropin are not made by the same process and there are differences in stability, solubility and absorption rates.[1] These factors may occasionally be of clinical importance. Some patients who seem to be maintained satisfactorily on a certain dose of one kind of corticotropin have a different response if a similar amount of another preparation is given. Because of this variability in potency, it has been suggested that human assay may be superior to animal assay.[82, 91]

Cortisone, a pure crystalline substance of known chemical structure, is of course assayed by weight. During initial investigational studies, some variation was noted in the potency of various batches of cortisone. This was believed due to "unstable suspensions."[52] This difficulty was quickly overcome. The reviewer is not aware of any reports in the past two years of variability in the potency of different preparations of cortisone.

MODE OF ACTION OF CORTICOTROPIN

Corticotropin acts by stimulating the adrenal gland to increase the synthesis and discharge of adrenal steroids. Recent evidence indicates that Compound F of Kendall, or hydrocortisone, is the principal hormone that is elaborated by the stimulus of corticotropin, along with smaller amounts of corticosterone and cortisone.[20, 73, 79, 87] Cholesterol, present in high concentration in the adrenal cortex, is probably the precursor of these steroids. It might be supposed that corticotropin, by stimulating the secretion of several adrenal steroids, may produce clinical effects other than those derived from cortisone. There is little evidence to date, however, to support this supposition.[52]

A given quantity of corticotropin may elicit a variable response in adrenal steroidal output. An inactive gland, for instance, in a person with long-standing hypopituitarism may show a subnormal response to the same dose of the hormone which may produce a large output of adrenal steroids from a normally active gland.[64, 102] It is also possible that a gland which may be already greatly stimulated by endogenous corticotropin as a result, for instance, of stress, may respond subnormally to an administered dose of the hormone. However, the observa-

tions of Roche and his colleagues are not in accord with this.[95] They performed Thorn tests on patients in the postoperative period. In this group, the eosinophils were already depressed because of the stress induced by operation, yet when corticotropin was given a further depression of the eosinophils occurred. These findings would seem to indicate that the normal adrenal gland has a considerable reserve secretory power.

RESISTANCE TO CORTICOTROPIN

Resistance to corticotropin may develop, particularly in the course of long-term therapy. This may be manifest by a worsening of the symptoms and signs of the disease under treatment, and by a diminished eosinophil response to the Thorn test.[2] Holbrook and his associates noted that the dose of corticotropin required to control the symptoms and signs of rheumatoid arthritis progressively increased in 12 of 35 cases.[55] They observed three types of resistance: (1) Primary—in which there was no clinical response even the first time corticotropin was given. (2) Acquired species specific—in which after a satisfactory initial response, increasing doses of pig corticotropin were required to maintain a satisfactory response; on changing to beef corticotropin, a dramatic clinical response occurred with the same or smaller doses. (3) Acquired, apparent nonspecific—in which patients who required increasing amounts of pig corticotropin needed the same or larger doses of beef corticotropin. The cause of the development of this resistance is not known. Forsham and co-workers expressed belief it is due to tissue inactivation rather than to antihormone development.[39] It is noteworthy, however, that the resistance which develops following administration of other pituitary hormones, such as the thyrotropic, gonadotropic and diabetogenic hormones, is generally considered to be due to the development of a specific antihormone. A patient who becomes resistant to corticotropin administered intramuscularly usually is responsive to the hormone when it is administered intravenously. Thorn and his colleagues reported they had not encountered the development of resistance to purified corticotropin.[113]

METHODS OF ADMINISTRATION

Cortisone may be given orally, subcutaneously or intramuscularly. The onset of effect of cortisone given by mouth is usually more rapid and the duration of action shorter than when it is administered intramuscularly. The effect when it is given by mouth usually lasts six to eight hours; when given intramuscularly, from 24 to 48 hours.[13, 115] It is advisable, therefore, when the hormone is administered by mouth, to give it in divided doses. The effective oral dose in 100 cases of rheumatoid arthritis studied by Ward and colleagues was equal to the intramuscular dose in about one-half the cases; in the other half about a sixth to a quarter more of the preparation was required when it was given orally.[115] Cortisone is rarely ineffective orally.

The method of administration as well as the dose of corticotropin greatly influences the adrenal response. The hormone is ineffective if given orally, as it is inactivated by gastrointestinal enzymes. A single dose of corticotropin given intramuscularly will produce a measurable adrenal response within thirty minutes. This will be maximal in four hours and will disappear in approximately twelve hours.[40] For continuous therapeutic control throughout the 24-hour period, it has been necessary to give corticotropin in divided doses every six to eight hours.

To obviate the necessity of multiple daily injections, long-acting preparations for intramuscular use exclusively have been made by the addition of substances which delay absorption of corticotropin from the site of injection.[122, 123] Gelatin is the menstruum currently used in commercial preparations. Some investigators are skeptical as to whether the long-acting preparations, given once or twice daily, are as therapeutically effective as the aqueous preparations given at four- to six-hour intervals.[56] Thorn and associates, however, expressed the opinion that purified corticotropin in gelatin, which has a sustained effect on the adrenal cortex for longer than 24 hours, is a very effective therapeutic agent.

Gordon[47] observed that 50 mg. of corticotropin given by constant intravenous drip results in a much greater adrenal stimulation than does 100 mg. of the same preparation given intramuscularly in 25 mg. doses at six-hour intervals. In fact, as little as 10 mg. of corticotropin given intravenously daily for ten days has produced many of the signs and symptoms of Cushing's disease.[77] The observations of Renold and his colleagues indicate the importance of the time factor in intravenous administration.[92] Twenty milligrams of corticotropin given in one minute produces no significant adrenocortical activity; the same dose given over a period of two days will triple the daily excretion of 17-ketosteroid. Twenty milligrams seems to be a critical dose. Increasing the amount administered intravenously in an eight-hour period above this figure does not significantly increase the adrenocortical response.

CUSHING'S SYNDROME

Before corticotropin and cortisone were available in substantial quantities for clinical investigation, some knowledge as to their physiologic effects was accurately predicted by studies of the various manifestations of Cushing's syndrome.[107] The features of this syndrome are a characteristic adiposity, diminished carbohydrate tolerance, hypertension, nega-

tive nitrogen balance, lymphopenia and eosinopenia, osteoporosis, acne, cutaneous striae and hirsutism. There is an increased urinary excretion of adrenal hormones. Susceptibility to infection and poor wound healing also occur. Mental disturbances are not uncommon. Most if not all of these features have been produced with large doses of cortisone and corticotropin given over prolonged periods of time. It is important to emphasize, however, that the changes induced by the hormones are nearly always reversible and disappear with cessation of treatment or reduction of the dose.

EFFECTS ON WATER AND ELECTROLYTE METABOLISM

Cortisone and corticotropin may have varying effects on water metabolism. There may be either retention or diuresis during hormone administration, depending upon the preexisting physiologic state. Such alterations are usually a consequence of changing plasma electrolyte levels. At times, however, a dissociation may occur between urinary excretion of water and of electrolytes.[113] Soon after hormone administration is begun there is a transient shift of water, sodium and chloride into the extracellular spaces. This reaches a peak within 8 or 9 days and then subsides as treatment continues. Cortisone in daily doses of 100 mg. will cause little if any change in the balance of calcium, phosphorus, sodium, potassium and chloride, and in the concentration of these ions in the blood.[107] Corticotropin in 100 mg. daily doses intramuscularly and cortisone in 200 mg. daily doses will regularly induce a negative balance of potassium. The effects on excretion of sodium and chloride are somewhat variable. Usually there is early retention of the ions, followed later by increased excretion.

EFFECTS ON CARBOHYDRATE METABOLISM

In the doses usually employed, cortisone and corticotropin ordinarily do not produce alterations in carbohydrate tolerance. Sprague and associates noted no significant changes in the fasting blood sugar levels in 16 patients with rheumatoid arthritis under treatment with cortisone.[107] In 14 of these patients, glucose tolerance tests were performed. In 10, the results were normal; in 4, abnormal curves were observed. Two of the patients with abnormal glucose tolerance were tested after cessation of treatment and had normal tolerance curves. The occasional occurrence of diabetes mellitus has been reported in patients whose carbohydrate tolerance both before and after treatment was normal.[19] The insulin requirement of diabetic patients has been observed to increase during the administration of these hormones.[12]

EFFECTS ON FAT METABOLISM

The most evident effect of these hormones on fat metabolism is an alteration in fat deposition, with the appearance of moon-shaped facies and fatty deposits in the cervicodorsal and supraclavicular areas.[109] Hypercholesterolemia has been observed during prolonged treatment with corticotropin and cortisone.[3, 93]

EFFECTS ON NITROGEN METABOLISM

Although cortisone has been shown experimentally to inhibit protein synthesis and to increase protein catabolism, the effects of therapeutic doses of cortisone on nitrogen metabolism in man have not been striking. One hundred milligrams a day causes little or no augmentation in nitrogen excretion, but 200 mg. a day of cortisone and 100 mg. a day of corticotropin intramuscularly cause a negative nitrogen balance.[107] A significant increase in urinary excretion of uric acid and a decrease in uric acid content of serum have been observed with the administration of cortisone in 100 and 200 mg. doses and with 100 mg. doses of corticotropin. This is particularly evident when the content of uric acid in the serum before the hormones are given is in the upper part of the normal range or elevated.[107]

CARDIOVASCULAR EFFECTS

Blood Pressure: There has gradually accumulated a large amount of evidence linking the adrenal cortex with hypertension.[83] Hypertension is a common occurrence in Cushing's disease; contrariwise, hypotension is frequent in Addison's disease. There has been some variance of opinion as to the effects of corticotropin and cortisone in humans. In normotensive patients with normal renal function, Perera found no significant variation in blood pressure occurring during cortisone administration.[85, 86] Dustan and colleagues confirmed this with regard to cortisone.[31] Corticotropin, however, in 60 to 200 mg. daily doses intramuscularly, increased the blood pressure of both normotensive and hypertensive persons. Hein and Whipple noted that "about half" of a group of 22 patients receiving rather large doses of corticotropin and cortisone had elevation of systolic pressure of 30 mm. of mercury or more, and of diastolic pressure of 10 mm. or more.[50] In hypertensive patients, especially those with impaired renal function, a further increase in blood pressure seems to be a common although not invariable occurrence during hormone administration.[103] On the other hand, the administration of cortisone to children with the adrenogenital syndrome may result in a very significant reduction in blood pressure.[121]

Capillary Permeability: Increased capillary resistance as measured by a negative pressure method has

been noted after various types of stress. Robson and Duthie measured capillary resistance in patients under treatment with corticotropin and cortisone. In most, there was an increase in capillary resistance.[94] In two cases of idiopathic thrombocytopenic purpura, Robson and Duthie noted an increase in capillary resistance although there was no change in the number of platelets. However, Bethell and colleagues,[10] and Jacobsen and Sohier[59] observed increases in the number of platelets in the blood of patients with thrombocytopenic purpura who were receiving either substance. On the other hand, easy bruising, presumably related to increased capillary fragility, has been noted during prolonged hormone therapy.

Thromboembolic Complications: Cosgriff and associates[23] observed a considerable shortening of the coagulation time of venous blood in patients under treatment with these substances. The mechanism of this alteration is not clear but it seems to be of some clinical importance. The incidence of thromboembolic complications, particularly thrombophlebitis and pulmonary embolism, in patients under treatment with these hormones or during the first three or four weeks following treatment, seems to be higher than it might logically be expected to be from the underlying disease process alone.[24] Fahey, however, could not confirm Cosgriff's observations; he noted no significant alteration of the coagulation time after the administration of either hormone.[35]

RESPIRATORY EFFECTS

Cortisone and corticotropin increase the vital capacity and maximal breathing capacity in several chronic pulmonary diseases, including bronchial asthma, emphysema, beryllium granulomatosis, silicosis and sarcoidosis. Investigation of these effects has been limited and the results have not been completely consistent.[44, 61, 117]

GASTROINTESTINAL EFFECTS

Gastric Secretion: Gray and associates[48] studied the effect of corticotropin on gastrointestinal enzymes and of cortisone and corticotropin on gastric secretion. They demonstrated that these substances cause an increase of about 200 per cent in basal and nocturnal secretion of acid and pepsin. In every instance, corticotropin increased the acid secretion to an amount usually associated with active duodenal ulcer. Similar gastric response may be brought about by cortisone. One patient under their observation who had been given cortisone had two perforated duodenal ulcers, a second a massive fatal gastrointestinal hemorrhage, and a third a massive gastrointestinal hemorrhage and duodenal perforation. The occurrence of such untoward complications has been confirmed by many investigators.

HEMOPOIETIC EFFECTS

Both cortisone and corticotropin may cause neutrophilic leukocytosis for short periods, and both bring about eosinopenia and lymphopenia.[114] With corticotropin, eosinopenia may continue as long as the hormone is given and for some weeks thereafter, or there may be a return to near normal levels even while corticotropin therapy continues. During prolonged administration of cortisone, a significant increase in circulating neurophils has been observed, but no significant decrease in lymphocytes and eosinophils occurs.[107] The prompt eosinopenic response to corticotropin has been utilized by Thorn as a test for adrenocortical function. Although it may be inaccurate in certain circumstances, it remains the simplest method of estimating adrenocortical function.[112] Reticulocytosis and increase in the number of erythrocytes may follow hormone therapy of several diseases in which anemia is present.[36]

EFFECTS ON ENDOCRINE GLANDS

Pituitary: Corticotropin and cortisone both inhibit anterior pituitary function. Cytologic changes, similar to those that occur in spontaneous Cushing's disease, have been noted in the pituitary gland in patients to whom the hormones were given.[65] It is believed by some investigators that these alterations are retrogressive in nature and are secondary to increased circulating adrenal hormones. Recently, Sayers and co-workers demonstrated diminished content of corticotropin in the blood of patients with adrenogenital syndrome who received cortisone.[113] Ingle,[58] in 1938, demonstrated that adrenal atrophy which developed in rats following cortin administration is a consequence of depression of adrenotropic function of the anterior pituitary. Evidence of pituitary depression may, therefore, be indirectly derived through determination of adrenocortical function, which can be more easily estimated than can pituitary function.

Adrenal: Corticotropin causes an increase in the size of the adrenal cortex. Histologically, a loss of fat and hypertrophy of the zona reticularis and the zona fasciculata occur. Cortisone causes a definite decrease in the size of the adrenal cortex. Pronounced atrophy of the zona reticularis and of the zona fasciculata has been observed.[81] Alterations in secretory activity parallel these anatomic changes. Corticotropin brings about prompt increase in the urinary excretion of both 17-ketosteroids and corticosteroids. Cortisone usually causes a decrease in the urinary secretion of 17-ketosteroids initially, followed by a gradual leveling off with continued treat-

ment. Corticosteroid excretion usually increases when cortisone is administered; with prolonged treatment, this usually levels off, but remains above the pretreatment levels.[107, 114]

Adrenal Insufficiency on Hormone Withdrawal: Following withdrawal of either of these substances, there may be a period of adrenocortical insufficiency of variable degree, which may last for a few days to as long as three months. This is usually more pronounced after cortisone treatment, but also occurs following corticotropin administration. It may be manifested clinically by asthenia, somnolence, anorexia or depression. The urinary excretion of adrenocortical hormones decreases sharply and there is a diminished response to the Thorn test.[108] Eliel and associates,[33] in studies of water and electrolyte changes following discontinuation of these hormones, observed substantial losses of sodium and chloride after both, indicative of adrenocortical suppression. For instance, one patient after receiving 100 mg. of corticotropin per day for 30 days, lost two and one-half times as much sodium and five times as much chloride as was retained during the period of hormone administration. This temporary period of adrenal suppression, although at times distressing to the patient, may be of little serious consequence. However, if during this period the patient should be subjected to the stress of a serious injury, operation or illness, the adrenal response might prove inadequate. Fatalities have occurred in cases in which cortisone was discontinued immediately before a surgical operation.[42] To avoid iatrogenic adrenal insufficiency, administration of cortisone should never be halted abruptly, but decreased gradually over a period of several weeks.

Thyroid: Depression of thyroid function has been observed in patients under treatment with both corticotropin and cortisone. There is a reduction in the uptake of radioactive iodine (I^{131}) by the thyroid gland and by a low serum protein-bound iodine. The basal metabolic rate is reduced to minus 15 per cent or lower in only one-third of the cases. The reason for this is that corticotropin and cortisone are both calorigenic; both increase basal oxygen consumption in man by a direct action which does not involve alterations in thyroid function. Thyroid depression during hormone treatment may, therefore, be more pronounced than the basal metabolic rate indicates.[53, 124]

ANDROGENIC EFFECTS

Hirsutism in female patients is a common complication of long-term cortisone and corticotropin therapy.[52, 97] Acne occasionally occurs, particularly in younger patients. It is believed that these changes are related to the androgenic activity of the adrenal hormones. Fortunately, other evidences of masculinization do not occur. The hirsutism is usually mild, consisting of a light growth of hair on the upper lip and chin and along the cheeks. Nevertheless, to some patients this has been the most objectionable complication of therapy with these hormones.

NEUROLOGIC AND PSYCHIATRIC EFFECTS

Convulsive Seizures: The electroencephalograms of patients with epilepsy may become more abnormal during cortisone therapy.[46] Also, abnormal changes have been noted in encephalograms of patients who previously had normal tracings, indicating that both corticotropin and cortisone influence electrical activity of the brain.[54] Further evidence of increased cerebral excitation is suggested by reports of convulsions in patients without a previous history of seizures.[30]

Psychiatric Disturbances: Mental disturbances are frequent complications of treatment with either hormone. Most common are mild deviations of mood, particularly euphoria, generally regarded by both patient and and physician as a beneficial effect. However, psychoneurotic responses and frank and alarming psychoses may also occur. Rome and Braceland[96] expressed belief that psychotic reactions will develop in patients who have made only marginal psychological adjustment in the past.[96] This has not, however, been the experience of Clark, Bauer and Cobb.[16] In reviewing their observations of major mental disturbances during cortisone and corticotropin therapy, they noted that none of their patients who became mentally or emotionally disturbed while on treatment had a history of major mental disease. Furthermore, systematic clinical study revealed no clue to enable them to anticipate the occurrence of psychiatric complications. They stressed the importance of close observation for the early detection of these mental disturbances. Some of the premonitory signs which have been noted include paresthesias in the frontal region of the forehead (usually described as a sense of heaviness, fullness or fuzziness), insomnia, restlessness and agitation in some, lethargy and apathy in others. Delusional ideas and frank psychotic behavior may be the initial symptoms. It may be noted that all ten of the patients reported upon by Clark, Bauer and Cobb were receiving moderately large doses of corticotropin. As yet, no correlation has been established between any metabolic change induced by these hormones and development of mental disturbances.

OSTEOPOROSIS

Osteoporosis is a common manifestation in Cushing's disease. As might be expected, it has also developed in the hyperadrenal state induced by corti-

cotropin and cortisone. It is difficult, nevertheless, to determine the actual potency of these hormones as osteoporosis-producing agents. First of all, comparisons of roentgenograms taken at various intervals in treatment are unsatisfactory due to variations in radiographic technique; secondly, many of the patients who have received these hormones had a considerable degree of osteoporosis before treatment was begun. For instance, in the five female patients treated for long periods with cortisone by DiMartini and associates,[28] who developed pathologic fractures, one or more factors commonly predisposing to osteoporosis were present. These were prolonged bed-rest, an active disease process and the postmenopausal state. That cortisone does not always have a deleterious effect on bone metabolism is suggested by the following case report of Thorn and co-workers: A 51-year-old woman with non-tropical sprue of 13 years' duration and severe, generalized osteomalacia, had bilateral, impacted, subcapital fractures of the femoral neck as the result of a fall. Despite the presence of severe bone disease, cortisone in 100 mg. daily doses was continued for a month and then at 50 mg. daily thereafter. There was considerable improvement in the patient's health and weight. Although there had been complete absence of healing during a period of five weeks prior to cortisone therapy, both fractures healed satisfactorily, and three months after bilateral hip nailing, no distinct fracture line was evident.[113]

EFFECTS ON WOUND HEALING

Ragan and associates were the first to point out that corticotropin and cortisone may retard wound healing, both in humans and experimental animals.[90] Similar findings were noted by Alrich and associates[4] in rats, and by Spain and co-workers[104] in mice that were pretreated with corticotropin and cortisone. The doses used by these investigators were proportionally much larger than those commonly employed clinically. Cole and associates[17] noted no retardation of wound healing in dogs given these hormones in proportionally smaller doses. Poor wound healing, as has been mentioned before, is a fairly common occurrence in Cushing's disease, and there have been several references in the literature to this occurrence in patients receiving corticotropin and cortisone. In some cases it was not clear whether it was owing to the therapy or to underlying disease. Rosenberg and associates,[97] for instance, mentioned 20 patients who had skin and muscle biopsies just before corticotropin treatment. In 16, the wound healed promptly; in 4, there was a delay in wound healing, but 3 of the 4 had a generalized inflammatory disease of the skin. Other observers[49, 52] have noted no delay in wound healing. Ford and Key, for example, observed no interference with wound healing following orthopedic operations in 20 patients who were receiving cortisone, generally in smaller than ordinary doses and for relatively short periods.[41] The experimental studies of Findlay and Howes may help to explain these divergent reports.[37] They studied the combined effect of cortisone and partial protein depletion in wound healing in rabbits. When 1.5 mg. of cortisone per kilogram of body weight was given to rabbits on a normal diet, only a slight delay in wound healing was noted. A similar retardation was noted in animals depleted of protein but not receiving cortisone. However, the administration of cortisone to protein-depleted rabbits caused serious delay in wound healing. Many of the cortisone-treated patients in whom this complication developed had chronic febrile diseases. Protein depletion undoubtedly occurs in such cases and may well have been a factor in prolonged wound healing.

EFFECTS ON BACTERIAL INFECTIONS

Cortisone and corticotropin may bring about defervescence and apparent clinical improvement in patients with bacterial infections even though bacteremia may still be present. Considerable experimental evidence indicates the hormones cause lessening of resistance to bacterial infections. Experimental infection of cortisone-treated rabbits with streptococci and of cortisone-treated rats with tubercle bacilli caused the death of the animals, whereas in untreated animals that were given the same doses of the organisms there were no demonstrable systemic effects.[75, 76] The Committee of Medical Research of the American Trudeau Society has recommended that these drugs not be used in patients with active tuberculosis, and used only with extreme caution in patients with possible latent tuberculosis.[7] It is the committee's recommendation that diagnostic examinations for tuberculosis be carried out on all patients in whom the use of these hormones is contemplated. Not only have cortisone and corticotropin been inculpated in the reactivation of old and apparently arrested tuberculosis, but several fulminating and fatal cases have been reported in which the x-ray films of the chest before treatment were considered normal.[43, 62] Recently, the Committee on Therapy of the American Trudeau Society reviewed the cases of 81 patients with tuberculosis who had received either cortisone or corticotropin or both. In 40 cases the course of the disease was unfavorable, in 10 favorable, and in 25 apparently not changed. The committee surmised that "a large number of cases with unsuspected tuberculous disease must have received these hormones without harmful

effect," and it concluded that reactivation of tuberculous infection does not invariably result from treatment with cortisone or corticotropin.[18]

ANTIPHLOGISTIC EFFECTS

That cortisone and corticotropin suppress inflammation has been amply documented by observations in a wide variety of diseases, particularly in the fields of arthritis, dermatology, ophthalmology, allergy and cardiology. Careful histologic studies indicated that all elements of inflammatory response to a variety of etiologic agents may be suppressed by these hormones; that vascular tone is better maintained and there is less endothelial damage; that diapedesis of leukocytes is consequently lessened and there is a reduction of exudate; and that margination or "walling-off" of the area of injury by cellular elements is diminished.[32, 74, 105]

Because of the evidence linking the adrenal cortex with inflammation, it is suggested that the hormone may suppress inflammation by interfering in some manner with antigen-antibody reaction.[118, 119] This problem has been investigated at great length, but the results have not been altogether consistent. It is generally agreed, however, that corticotropin and cortisone do not interfere with antigen-antibody union, although they may inhibit the development of antibodies. Fischel[38] and Daugherty[26, 27] expressed doubt that inhibition of antibody formation is an adequate explanation for the anti-inflammatory properties of the hormones, for the amount of corticotropin required for complete suppression of circulating antibodies is far greater than that required to diminish allergic inflammation. Daugherty[27] concluded that cortisone diminishes inflammatory response to traumatic, bacterial and chemical as well as to allergic stimuli, not through some mechanism related to antigen-antibody union, but rather by a "specific antiphlogogenic action of its own." Although this cannot be accepted as a final answer, it seems to be a reasonable working hypothesis until knowledge of the manifold actions of these hormones is more complete. Precise information is still lacking, but the locus of the inflammatory action of the hormones is probably the tissue cell. Corticotropin and cortisone do not destroy or inhibit etiologic agents, but they so alter cellular physiology that the tissues are unable to sustain an inflammatory response. It is important to note that these hormones suppress both "useful and useless" inflammation with impartiality. The suppression of inflammatory response to bacterial infection is, of course, undesirable; the inhibition of the apparently useless inflammatory response of rheumatoid arthritis or a non-specific iritis is very desirable.

INCIDENCE AND IMPORTANCE OF UNDESIRABLE EFFECTS

How often do undesirable physiological effects occur? The overall incidence in several large series, including many cases in which treatment was continued over a long term, has been between 40 per cent and 66 per cent.[11,97,110,111] It is important to emphasize that many of these undesirable reactions are of little consequence and do not interfere with treatment. In none of 100 carefully selected cases of rheumatoid arthritis in which Ward and co-workers administered cortisone therapy was it necessary to discontinue treatment because of side effects; in only 10 per cent to 20 per cent of cases in which long-term treatment was given have such effects forced discontinuation of treatment.[67, 115, 116] To avoid these reactions or keep them to a minimum it has been frequently necessary for the clinician to strike a compromise between desired therapeutic result and adverse reactions by using amounts of these hormones which only partially suppress the disease process under treatment. It is pertinent to note at this time that the incidence of side effects is influenced by the daily dose employed and the sex of the patients. In the experience of Ward and co-workers,[115] side effects occurred in 63 per cent of patient receiving 75 mg. a day, compared with only 12 per cent in those receiving less than 75 mg. daily. Among patients receiving 75 mg. daily, side effects developed in 50 per cent of the men, in 72 per cent of the premenopausal women and in 85 per cent of the postmenopausal women.

Copeman[21] noted a tendency to attach undue importance to mild side effects: "The preoccupation of many observers to mild side effects reminds one of a house-proud woman over-conscious of a speck of dust which the visitor has not noticed." It is certainly true that the adverse reactions from these hormones have received very wide publicity in countless case reports, reviews and even monographs.[20, 111] Such reports may have partially obscured the numerous cases in which these hormones have been employed successfully. In some instances they have been life-saving; in others they have restored invalids and semi-invalids to a much happier, useful state. The use of any potent medication carries with it a calculated risk. After four years of clinical trial, it seems evident, nevertheless, that physicians who have some understanding of the protean actions of cortisone and corticotropin and who accordingly select patients and observe them carefully, can employ the hormones with great advantage and small risk.

511 South Bonnie Brae.

REFERENCES

The full list of 125 references may be obtained from the author.

CASE REPORTS

- **Streptokinase-Streptodornase Therapy of Sterile Postpneumonic Empyema of Long Standing**
- **Nephrogram Following Acute Myocardial Infarction**
- **Coronary Insufficiency Following Intravenous Pyelography**

Streptokinase-Streptodornase Therapy of Sterile Postpneumonic Empyema of Long Standing

EDGAR ROSEN, M.D., Oakland

STREPTOKINASE-STREPTODORNASE (VARIDASE®) consists of two streptococcal enzymes that promote liquefaction and absorption of fibrin and purulent exudate. Streptodornase acts directly upon desoxyribonucleoprotein and desoxyribonucleic acid, which constitute a large portion of the sediment in purulent exudates. Streptokinase leads to essentially the same end result on fibrin, although it acts in a more indirect manner by catalyzing a fibrin-lysing system normally present in human serum. Encouraging results have been obtained by the use of these enzymes in combination for the removal of fibrin and pus in various pathological states.[4, 5, 6]

Tillett, Sherry and Read[7] reported upon the usefulness of this therapy in the treatment of postpneumococcic empyema.

In the case herein reported, streptokinase-streptodornase was rapidly effective against empyema of long duration after prolonged unsuccessful administration of customary treatment.

From the Veterans Administration Hospital, Oakland.

CASE REPORT

A 47-year-old Negro male laborer was hospitalized on February 21, 1952, because of acute respiratory illness of four days' duration. Symptoms included fever, shaking chills, sweating, headache, dyspnea, pleuritic pain in the right side of the chest and severe cough productive of more than a cupful a day of thick yellowish-green sputum which was frequently blood-streaked. In addition, the patient complained of swelling and soreness of the left foot since the onset of this illness. Except for several self-administered patent medicines, there had been no treatment up to the time of admittance to hospital.

The past history was vague. The patient said that ever since discharge from the Army in 1943 he had had a continuous "cold," manifested by chronic cough, usually productive of about two ounces of sputum daily, occasionally blood-streaked. Concomitantly he had intermittent ill-defined pain low in the chest on both sides, frequent headaches, occasional feverishness, chilly sensations and sweating. There had been no known exposure to tuberculosis. No history of previous arthritis was obtained.

The patient was normally developed, slender, poorly nourished, very dyspneic, extremely restless and apprehensive. Respirations were shallow, labored and numbered 60 per

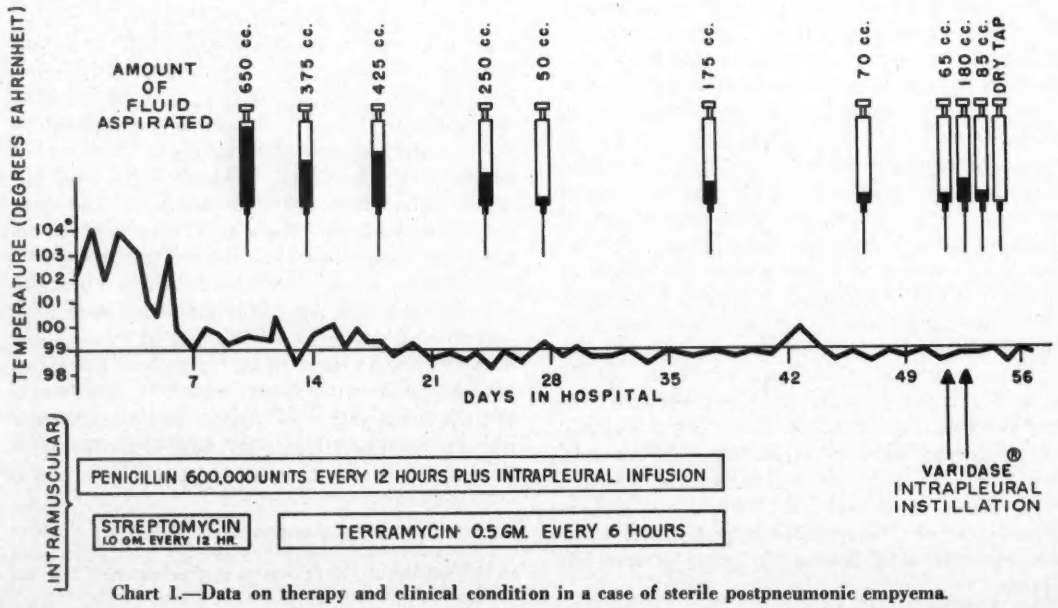

Chart 1.—Data on therapy and clinical condition in a case of sterile postpneumonic empyema.

minute. The rectal temperature was 102.2 degrees F., the pulse rate 128, and the blood pressure 94 mm. of mercury systolic and 60 mm. diastolic. Upon auscultation of the chest, evidence of extensive consolidation in the right middle lobe and of lesser involvement of the right lower lobe was noted. On the right side of the chest there were a respiratory lag, numerous fine to medium moist rales, dullness to percussion and bronchovesicular breath sounds. The left lung was clear. The heart sounds were normal except for sinus tachycardia.

Slight swelling, tenderness to palpation, increased heat, limitation of motion and slight erythema over the dorsal aspect were noted upon examination of the left foot. No inflammatory changes were noted in any other joints. There was slight clubbing of the fingers.

In roentgenograms of the chest dense consolidation of the middle lobe and moderate pneumonic density in the lower lobe of the right lung were noted. Films of the left foot showed no abnormality. Erythrocytes numbered 3.4 million per cu. mm. of blood and the hemoglobin content was 11.3 gm. per 100 cc. (both of these values rose to within normal limits later). Leukocytes numbered 2,950 per cu. mm. and the differential was 74 per cent segmented polymorphonuclear cells, 17 per cent band forms, 6 per cent lymphocytes, and 2 per cent metamyelocytes. Four days later leukocytes numbered 20,300, with 81 per cent segmented polymorphonuclear cells and 10 per cent band forms. Pneumococci of Type 7, sensitive in vitro to penicillin, streptomycin, oxytetracycline and chloramphenicol,* grew on a culture of blood. A test for cold agglutinins was negative. There was a heavy growth of hemolytic Staphylococcus albus on a culture of the sputum. In two examinations of sputum concentrates no acid-fast bacilli were observed. The content of uric acid in the blood was 3.4 mg. per 100 cc. and of bilirubin in the serum 0.91 mg. per 100 cc.

Therapy with penicillin given intramuscularly was begun the day of admittance, was supplemented by streptomycin the following day, and later by oxytetracycline (Terramycin®), as shown in Chart 1. During the first week the temperature was high (see Chart 1) and the patient was delirious. The following week, delirium and respiratory symptoms subsided. Thereafter, despite the development of empyema, there were no complaints except of residual soreness in the left foot for several weeks. Low grade fever continued during the second and third weeks, after which the temperature became normal.

Very little change was noted in roentgenograms of the chest taken five days after admittance, but films on the tenth hospital day showed a large encapsulated area of empyema lying mainly posteriorly. Thoracentesis was carried out from time to time thereafter (see Chart 1) and varying amounts of purulent cloudy tan fluid without any perceptible odor were withdrawn. Numerous cultures of this material showed no growth. Stained smears showed large numbers of polymorphonuclear cells, but no organisms were seen. The specific gravity of the fluid ranged from 1.020 to 1.022, and the protein content from 4.20 gm. to 5.20 gm. per 100 cc.

Combined systemic antibiotic therapy was continued up to the 38th hospital day, in addition to the injection of 100,000 units of crystalline penicillin into the empyemic cavity after each withdrawal of fluid. At first there was gradual reduction in the area of empyema but after several weeks it remained unchanged at approximately half its original size (Figure 1, *A*). Owing to the persistence of a large empyemic pocket (Figure 1, *B*) after six weeks, surgical excision was considered, but it was decided first to try intrapleural infusion of streptokinase-streptodornase. On the 52nd hospital day, 42 days after empyema was first noted, 65 cc. of empyemic fluid was aspirated and one vial of Varidase (streptokinase 100,000 units and streptodornase 25,000 units) dissolved in 20 cc. of normal saline solution was instilled into the empyemic cavity. Twenty-four hours later roentgenograms showed no appreciable change, and when thoracentesis was carried out 180 cc. of fluid much more turbid than that withdrawn the preceding day was aspirated. A second vial of Varidase was instilled and the following day 85 cc. of very turbid salmon-colored sanguineous fluid was aspirated. Roentgenograms taken immediately after this procedure showed a remarkable change. The right lung was now completely expanded and the empyemic cavity had disappeared, leaving only residual pleural thickening along the right lateral wall of the chest (Figure 1, *C*).

During the period of enzyme administration there was no fever but the patient complained of pronounced weakness, headache, nausea and vomiting. These symptoms subsided after the completion of enzyme therapy, and there were no further complaints.

Thereafter no further accumulation of fluid was observed in roentgenograms and the patient was discharged on April 23, 1952. He remained asymptomatic after leaving the hospital and roentgenograms six weeks after discharge showed practically complete resolution of the pleural thickening in the right side of the chest (Figure 1, *D*).

DISCUSSION

In view of the six weeks' duration of empyema in this case, it is of interest that so good a result was obtained with streptokinase-streptodornase therapy. In a previous series of patients treated with this agent for sterile postpneumococcic empyema, Tillett and associates[7] noted no definite benefit in two patients treated on the thirtieth and forty-second days of disease. It was felt that the poor result was owing to extensive cellular organization that had, presumably, taken place by then. Inasmuch as the enzymatic action of this agent is not effective against living cells, it is most advantageously employed before the suppurative process has progressed to the formation of organized tissue. The reason for the successful result in the present case is uncertain, but it may be postulated that little organization had taken place despite the prolonged duration of the empyema.

The optimal time for employment of this therapy has not been clearly established, but it seems reasonable that it should be used as early as clinical judgment will permit. Unfortunately, decision as to when to begin such treatment is often complicated by the fact that many patients in whom empyema eventually develops are at first critically ill with pneumonia, often accompanied by bacteremia. In these circumstances treatment of the patient takes precedence over treatment of the empyema, and injection of enzymes may wisely be postponed until the pneumonia and systemic toxicity have been controlled to some degree by antibiotics.

The variations in the problems encountered and the limited experience thus far accumulated have made it impossible to formulate any uniform rules for guidance in the enzymatic treatment of empyema. The optimal dosage and frequency of enzyme infusions must depend upon careful appraisal of the clinical situation in its entirety, coupled with knowledge concerning the basic action of the enzymes. Other standard therapeutic measures must be employed concurrently as indicated, including antibiotics to combat active infection, and suitable provision for drainage. Successful enzymatic action may be expected to produce increased amounts of liquefied purulent material, which should be removed from the pleural cavity as completely as possible. This may be accomplished by thoracentesis performed approximately eight to twenty-four hours after enzyme infusion, or by surgical means. Miller and co-workers[2, 3] advo-

*The typing of the organism and the sensitivity studies were performed through the courtesy of Dr. Lowell A. Rantz, at the Department of Bacteriology of the Stanford University School of Medicine.

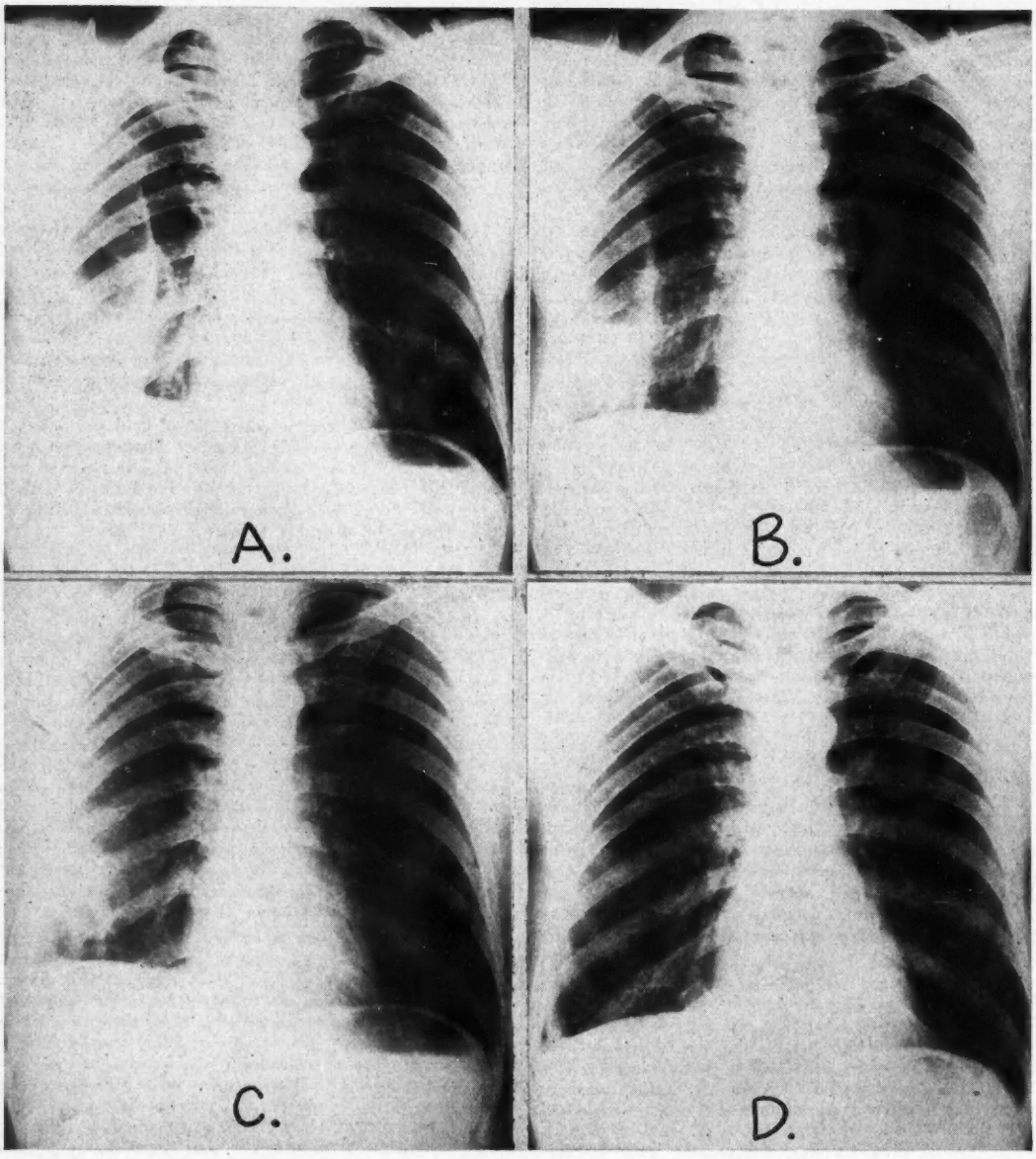

Figure 1.—*A.* (March 24, 1952) Large empyemic pocket persistent after three weeks of antibiotic therapy and thoracentesis. *B.* (April 14, 1952) Only slight reduction in size after an additional three weeks. *C.* (April 16, 1952) Following two daily injections of Varidase, the empyemic cavity has disappeared, leaving only residual pleural thickening. *D.* (June 16, 1952) Normal roentgenogram except for minimal pleural thickening.

cated the routine use of intercostal closed catheter drainage, with the tube kept clamped for as much as eight hours after instillation of enzymes but opened sooner if untoward toxic manifestations appear.

The toxic reactions[4] thus far observed have in general been transitory and not of serious consequence. Leukocytosis has been frequently observed, as well as febrile reactions which may be accompanied by systemic symptoms such as headache, myalgia or arthralgia, malaise, nausea or vomiting. Minor transient urinary abnormalities have also been noted. Questionable allergic reactions have been described in only a few instances. Circulatory collapse in a patient with pleural effusion was reported by Baum and Oransky,[1] who attributed it to anaphylactoid reaction. However, this interpretation was later questioned by Miller and Long[2], who emphasized that the sudden accumulation of large amounts of fluid in the pleural space could lead to mediastinal displacement and cardiorespiratory embarrassment.

SUMMARY

In a case of sterile postpneumococcic empyema rapid resolution of the lesion occurred upon intrapleural instillation of streptokinase-streptodornase, following six weeks of unsuccessful conventional management.

447 Twenty-ninth Street.

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Nephrogram Following Acute Myocardial Infarction

HYMAN PECK, *M.D.*, Los Angeles

THE TERM NEPHROGRAM denotes opacification of the roentgenographic renal shadows owing to the presence of contrast media in either the finer elements of the renal vasculature or the various segments of the nephron or both. Nephrograms were first observed in cases of obstructive uropathy.[2, 5] In such conditions the increased intrapelvic pressure causes a decrease in glomerular filtration but does not interfere with the flow of the medium across the tubular epithelium into the lumina where, since it cannot be excreted, it concentrates.[2]

The radiographic demonstration of vessels in renal parenchyma was first noted as an incidental finding during angiocardiography.[4] It may occur also during translumbar aortography. These procedures result in high concentrations of the medium in the blood in the renal vessels. Nephrograms may occur in association with a reduction in blood pressure during intravenous pyelography, as was reported by Wickbom.[6] In the two cases in which Wickbom observed the phenomenon the decrease in blood pressure was thought to be due primarily to the use of a compression band on the aorta and perhaps secondarily to a reflex in the autonomic nervous system.

In the case to be reported here, no compression was used and nephrogram occurred in association with a decrease in blood pressure owing to acute myocardial infarction.

CASE REPORT

A 67-year-old white male with a diagnosis of hypertensive cardiac disease was referred for intravenous urography with the additional diagnosis of benign prostatic hypertrophy with symptoms of urgency and frequency of urination, nocturia and dribbling. Twenty cc. of 35 per cent Diodrast® was given intravenously following negative result of an intradermal test for Diodrast sensitivity. Approximately 20 minutes later the patient was in a state of shock. An electrocardiogram made within an hour showed posterior myocardial infarction. The blood pressure at this time was 60 mm. of mercury systolic and 50 mm. diastolic. In subsequent review of films it was noted that kidney and psoas shadows were plainly visible on a film (Figure 1) taken before the administration of Diodrast. Renal opacification with only minimal dye in the urinary bladder and none in the pelves and calyces was seen on subsequent serial films at 5, 10, 15 and 25 minutes (Figure 2).

From the Veterans Administration Center, Los Angeles, and the Department of Radiology, School of Medicine, University of California Medical Center, Los Angeles.

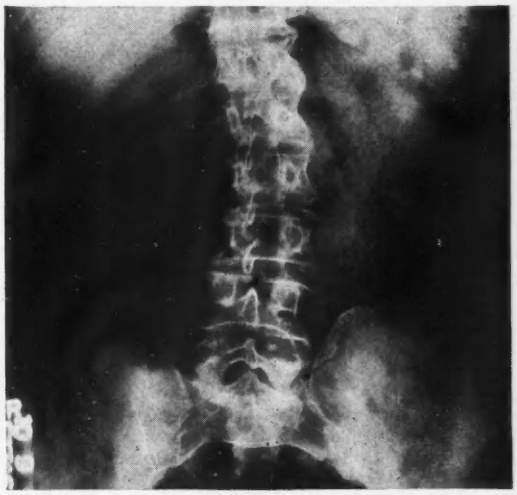

Figure 1.—Preliminary film of abdomen taken before intravenous urography, showing kidney and psoas shadows.

Figure 2.—Nephrogram. Kidney shadows are opacified.

DISCUSSION

It is known that urinary filtration stops when the arterial systolic blood pressure decreases to 60 mm. of mercury, as it did in the present case owing to myocardial infarction. With the arterial pressure at that level the pressure in the afferent arterioles is about 36 mm. of mercury and the orthostatic pressure is approximately equal to the pressure in the renal calyces (about 5 mm. of mercury) when the osmotic pressure of albumin in the blood (30 to 40 mm. of mercury) is taken into account.[1]

SUMMARY

Opacification of renal shadows during intravenous urography may occur in the presence of a decrease in blood pressure. A case in which a nephrogram resulted from decreased pressure owing to acute myocardial infarction is reported.

Veterans Administration Center, Los Angeles 25.

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Coronary Insufficiency Following Intravenous Pyelography

CARL C. EPSTEIN, M.D., Oakland

As WITH MANY another valuable diagnostic procedure, some risk, although statistically slight, is entailed in intravenous pyelography. In 1942, Pendergrass and co-workers[2] became interested in this subject as the result of the death of a patient following an injection of Diodrast.® They sent three thousand questionnaires to radiologists and urologists in the United States and Canada, and the replies revealed 26 deaths following Diodrast injection in addition to 11 that already had been reported. Since then there have been additional reports of death from this cause.[1, 6] The survey by Pendergrass also revealed that non-fatal reactions occasionally occurred following pyelography, some minor in nature, others more alarming. In the following case there was an unusual sequence of symptoms in a patient following pyelography, specifically a reaction consisting of pain in the chest and electrocardiographic evidence of coronary insufficiency.

CASE REPORT

A 57-year-old white male carpenter was admitted to hospital Jan. 14, 1953, with a presumptive diagnosis of carcinoma of the stomach based on roentgenograms taken by a physician in private practice. The patient related that on December 23, 1952, he had had "flu" and had been given penicillin by mouth for three days. A week later he was told that he looked anemic. Laboratory studies, the patient said, had shown "hemoglobin below 62" and blood in the stool. Carcinoma of the stomach was diagnosed on the basis of some irregularity about the pylorus noted in a gastrointestinal series.

Questioning of the patient elicited no indication of symptoms referable to the gastrointestinal tract. He had noted no lessening of appetite and there had been no loss of weight.

Six years previously he was refused insurance because of albumin in the urine, and in early December, 1952, he was rejected as a blood donor when, for the first time, he was told that his blood pressure was high.

Upon physical examination the patient appeared to be well nourished and in no distress, but the skin was distinctly sallow. The temperature, pulse and respirations were normal. The blood pressure was 192 mm. of mercury systolic and 102 mm. diastolic. The radial arteries were slightly thickened, and the arterioles of the ocular fundi were narrowed and tortuous. The heart tones were normal except for slight accentuation of the second aortic sound. The lung fields were clear to auscultation. No masses, enlargement of organs or tenderness were noted in palpation of the abdomen. No abnormalities were noted in digital examination of the rectum and prostate.

Erythrocytes numbered 2,800,000 per cu. mm. of blood and the hemoglobin content was 9.3 gm. per 100 cc. The number of leukocytes and the differential were within normal range. Urinalysis showed a trace of albumin, and upon microscopic examination a moderate number of hyaline, granular, and epithelial casts was noted. A urine concentration test showed a fixed specific gravity of 1.010. The urea nitrogen content of the blood was 49 mg. per 100 cc. at the time of admittance and a week later it was 60 mg. per 100 cc. Results of additional studies of the blood were as follows: creatinine, 4.5 mg. per 100 cc.; carbon dioxide combining power, 41 volumes per 100 cc.; total proteins, 6.3 gm. per 100 cc., with 4 gm. albumin and 2.3 gm. of globulin per 100 cc.; calcium 11.2 mg. per 100 cc.; phosphorus 4 mg. per 100 cc.; glucose (fasting) 105 mg. per 100 cc. The result of a Kahn test was negative for syphilis.

In an electrocardiogram there were inverted T waves in aVL and low amplitude T waves in V-6, suggesting myocardial disease of the lateral wall (Figure 1, A).

No abnormalities were noted in a roentgenogram of the chest. In roentgen study of the upper gastrointestinal tract an ulcer crater in the pyloric region of the stomach, with adjacent mucosal inflammatory changes, was noted. An intravenous pyelogram, described below in detail, failed to produce satisfactory visualization due to poor excretion of the dye.

The patient was treated with a conventional "ulcer regimen" and remained free of digestive complaints. Healing of the ulcer crater was observed in later roentgen studies.

It was felt that the patient also had chronic nephritis of unknown cause, and further diagnostic studies were requested. Intravenous pyelography was carried out on January 28, 1953, with 20 cc. of 75 per cent Neo-Iopax® used as the contrast medium. The customary procedure for intravenous pyelography at this hospital is to inject 1 cc. of the dye, wait one minute, and, if no untoward reaction or symptoms develop, inject the remainder of the dye over a period of one to two minutes. The patient received the dye at 9:30 a.m. without any difficulty, and roentgenograms were taken

From the Veterans Administration Hospital, Oakland.

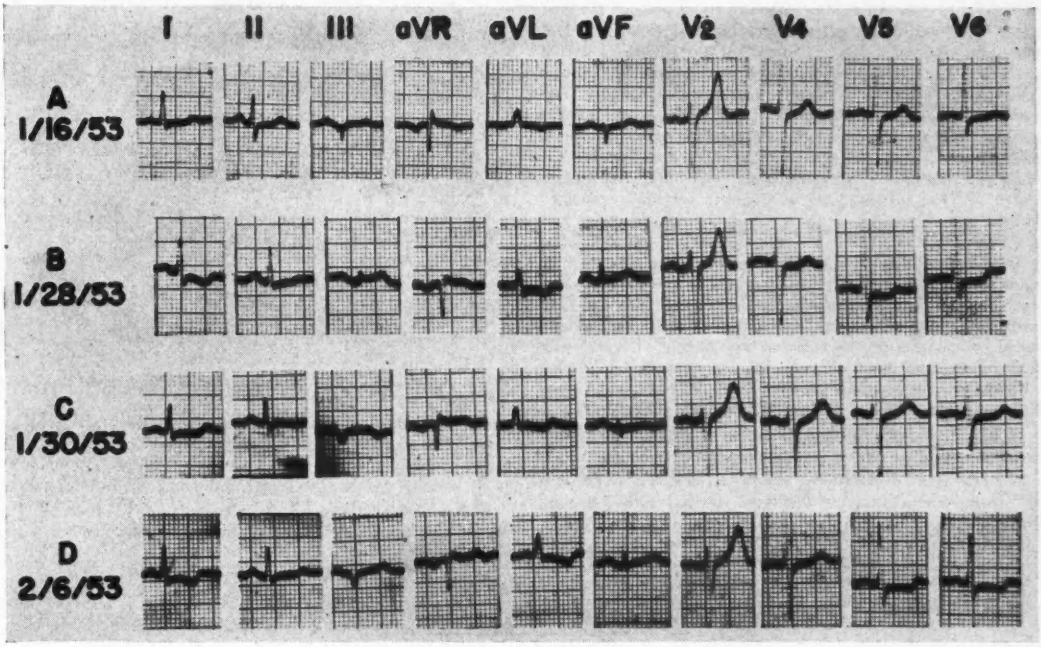

Figure 1.—*A.* Electrocardiogram taken before intravenous pyelography shows an inverted T wave in aVL and low amplitude T wave in V-6 suggesting lateral wall disease. *B.* Electrocardiogram taken about two hours after dye injection and one hour after onset of thoracic pain shows distinct ST segment depression in leads 1, aVL, V-4, V-5 and V-6 compatible with coronary insufficiency. *C.* Two days after reaction: Less ST segment depression in left precordial leads and appearance of T wave inversion in leads 3 and aVF. *D.* Nine days after the reaction: Slightly more ST depression in left precordial leads with T waves now upright in leads 3 and aVF.

at three, ten, and twenty minutes after dye injection with a compression bag over the lower abdomen, and at twenty minutes with the patient upright without the compression bag. The patient was returned to the ward at 10 a.m. and ate breakfast. A few minutes later he vomited, and a shaking chill lasting about one-half hour then occurred. It was followed by a "pressing" pain in the anterior chest that radiated into both arms and was accompanied by dyspnea. The heart tones were normal, the pulse rate was 92, and the blood pressure was 220 mm. of mercury systolic and 120 mm. diastolic. A hypodermic injection of 100 mg. of meperidine hydrochloride was given and the pain subsided gradually over a period of about an hour. Thereafter the patient remained free of pain and had no other complaints. Four hours after the chill, the temperature was 99.6 degrees F., but it then declined and remained normal.

An electrocardiogram taken approximately two hours after the injection of the dye (one hour after the onset of thoracic pain) revealed ST segment depressions in leads 1, aVL, V-4, V-5 and V-6 (Figure 1, B). This, when compared with the tracing made before intravenous pyelography (Figure 1, A) was compatible with a diagnosis of coronary insufficiency. An electrocardiogram two days after the intravenous pyelography showed less ST depression in the left precordial leads and the appearance of T-wave inversion in leads 3, and aVF (Figure 1, C). A week later a fourth electrocardiogram continued to show slightly more ST depression in the left precordial leads with the T waves again becoming upright in leads 3 and aVF (Figure 1, D).

COMMENT

Reactions following intravenous pyelography have been attributed to hypersensitivity to or toxicity of iodine, the differentiation for the most part being very difficult. Immediate deaths have been considered as owing to anaphylactic reactions; delayed deaths as owing to toxic reaction. The non-fatal reactions include purely local manifestations of the intravenous injection itself, such as pain, burning, numbness of the arm and shoulder, probably due to venospasm and occasionally venous thrombosis; or generalized symptoms such as flushing, nausea and vomiting, itching, urticaria, rhinitis, lacrimation, salivation, sense of constriction in the larynx, cerebral irritation, syncope, shock, chills, fever, and tachycardia. Singer,[7] who reported general reactions in 61 of 160 cases, distinguished allergic symptoms, such as urticaria, edema, asthma, rhinorrhea, and sneezing, from neurovascular manifestations such as flushing, nausea and vomiting, syncope, pallor, and sense of constriction (not further elaborated). Robins[8] grouped reactions into three different categories: (1) Psychogenic, with symptoms of nervousness, restlessness, faintness, numbness and tingling of extremities, nausea, and pain in the back—patients with reaction of this type responding well to reassurance; (2) autonomic or neurovascular, consisting of facial flushing, pallor, cyanosis, evidence of peripheral vascular failure, sweating, dilation of pupils, coldness of extremities, tachycardia, rapid respirations, nausea and vomiting—these symptoms usually occurring during or shortly after intravenous administration of the dye, usually being mild, although occasion-

ally severe; (3) allergic, consisting of urticaria, rhinitis, sneezing, wheezing, difficulty in breathing, conjunctivitis, and edema of eyelids and face. Naterman and Robins[2] felt that there was no reliable method of determining whether or not a reaction was due to allergic sensitivity. Accordingly, any symptom following injection of Diodrast was considered a general reaction. In the series of cases studied by Naterman and Robins, 81 of 404 patients had reactions that for the most part resembled those reactions or symptoms described above. It was of interest, as regards the case reported herein, that three (3.7 per cent) of the patients who had reactions were described as having "chest symptoms": one patient vomited, coughed and choked for a few minutes very soon after the injection; another choked, coughed, became cyanotic and "brought up yellowish fluid"; the third choked and showed evidence of cardiovascular collapse. The authors made no mention of any coronary component of these reactions. Pritchard[4] mentioned among the reactions following intravenous pyelography the symptom of "slight precordial tightness" but did not discuss the symptom further.

It is not the purpose of this report to discuss why these reactions occur or how to prevent them. A review of the various methods of determining sensitivity suggests unpredictability in the correlation between testing and reaction. Nevertheless, there is uniformity in opinion that the procedure is hazardous in highly allergic, severely uremic, or severely jaundiced patients.

SUMMARY

A case of coronary insufficiency following intravenous pyelography is presented, as well as a brief review of various types of reactions and symptoms which may follow such a procedure.

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Voluntary Health Insurance

THE AMERICAN PEOPLE voluntarily increased their protection against the unexpected costs of hospital, surgical and medical care to new record high levels in 1952, the Health Insurance Council reported in its annual survey of accident and health coverage in the United States. Every section of the country participated in the gains, the Council said.

Cash benefits flowing from voluntary health protection aggregated more than $2 billions in 1952, the Council reported. About half this amount went to help meet the cost of hospitalization, and over a half billion dollars more went toward operations and doctors' bills. Another half billion dollars represented benefit payments by insurance companies replacing income lost due to accident or sickness. Thus voluntary health protection is now taking care of a substantial part of the nation's health bill, the Council stated.

The total number of persons covered against hospital expense approached the 92-million mark at the end of last year, an increase of more than 5½ million, or 7 per cent, over 1951.

More than 73 million persons were protected against the cost of operations under surgical expense coverage at the end of 1952, the Council said, an increase of more than 7½ million persons, or 12 per cent, over the year before.

Approximately 8 million more persons than in 1951 were protected against doctors' bills under medical expense coverage at the end of last year. This increase brought the total number of persons so protected to nearly 36 million and represented an increase of 29 per cent over 1951.

The year likewise saw increasing public acceptance of major-medical expense coverage, the newest form of voluntary health protection designed to help meet the catastrophic costs of very serious illness. Nearly 700,000 persons had this form of protection at the end of last year, the Council stated.

Copies of this report may be obtained from the Health Insurance Council, 488 Madison Avenue, New York 22, N. Y.

California MEDICINE

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For information on preparation of manuscript, see advertising page 2

EDITORIAL

The Interim Session

ON DECEMBER 12 AND 13 the California Medical Association will hold its 1953 Interim Session of the House of Delegates. While interim sessions have been held in two previous years, this one may be different—it may be the last of its kind except in event of pressing need.

The first Interim Session of the House of Delegates was held in 1951, under terms of the revised Constitution and By-Laws adopted at that year's annual session. It was frankly experimental and it is obvious that the proponents of these winter meetings had various reasons for favoring them.

In the rewriting of the Constitution and By-Laws, a job that took two years and numerous meetings, arguments were advanced for writing into the By-Laws a provision for a mandatory session of the House of Delegates between the annual session meetings. Some proponents expressed the belief that the business of the Association had grown to the point where decisions could not be deferred for a full year. Others felt that the C.M.A. Council, which acts officially between meetings of the House, too often had to make decisions on matters that might better be considered by the House. Still others believed that more frequent meetings of the House would bring about a spirit of closer kinship between the delegates from all parts of the state.

Whatever the reason, the Interim Session became a part of the C.M.A. official procedure in 1951 when the revised Constitution and By-Laws were approved and put into effect.

With its first meeting, the Interim Session heard resolutions which would do away with it. Delegates who believed an annual meeting was sufficient sought to rid the Association of the mandate for a mid-year business session. Their contention was not approved by the House, probably on the basis that the Interim Session should be given a fair trial before its doom was considered.

In each succeeding session the same question has been raised. Both annual and interim sessions of the House have considered renewed proposals to abandon the rule that the Interim Session must be held and to rely upon the existing provision that special sessions may be held, upon recommendation by the Council or upon petition from delegates themselves.

For technical reasons, if none other, these proposals did not succeed until the 1953 Annual Session, when the House of Delegates passed amendments which set up machinery for calling an Interim Session only when such a meeting is deemed necessary. Under existing By-Laws an Interim Session will not be held in any year unless the Council recommends in advance of the Annual Session that the Interim Session be held that year.

This provision undoubtedly does not satisfy those who believe the Council's authority in the management of the Association's policies between meetings of the House is too great. It probably does satisfy those who feel that an Interim Session is not needed every year.

If the Council does not recommend an Interim Session, this inaction will certainly result in clarifying a situation in which there had come to be considerable confusion as to what business before the House was to be acted upon immediately as an emergency and what postponed until the next meeting.

Under the system of two House meetings each year, the theory was that business introduced at any session would be held over for consideration at the next meeting. This plan was supposed to eliminate hasty or ill-advised action on an official basis. At the same time, provision had to be made for immediate action by the House on matters of immediate importance; therefore, it was decided that business deemed of an emergency nature could be introduced

and acted upon at the same session of the House of Delegates.

In practice, this emergency provision would appear to have been overused. Any delegate needed only introduce his resolution as an emergency and his fellow delegates would sympathetically agree that the matter should be voted on at that session. Their agreement was more a consent to take immediate action than a recognition of a real emergency in the subject of the resolution.

The original concept of the drafters of the revised Constitution and By-Laws was that the six-month period intervening between meetings of the House would allow time for mature consideration of business. As the plan operated, the business referred to a reference committee at a meeting of the House was considered at the time of the meeting at which it was introduced and the committees drew up tentative reports, subject to amendment if opinions submitted in the next six months were such as would alter the tentative recommendation. Actually, the committees received almost no correspondence concerning any of the held-over business.

It should be noted that the House of Delegates of the American Medical Association has been holding interim sessions for the past six years. It should also be noted that many A.M.A. delegates feel that this session is not needed and is nothing more than a time-consuming demand upon them. In its development, the A.M.A. Clinical (or interim) Session has become much more important as a scientific clinical session than as a business meeting.

The California Medical Association has given this idea a trial, a trial which may terminate next month. The action of the House of Delegates in leaving the question of future interim or special sessions up to the recommendation of the Council, or to petition by a majority of the delegates, would seem to indicate that the time-honored system of annual sessions, with the Council acting officially between such sessions, will continue to be a satisfactory way of handling the affairs of the Association.

CALIFORNIA MEDICAL ASSOCIATION INTERIM SESSION

SCIENTIFIC PROGRAM

SATURDAY, DECEMBER 12, 1953

"Tuberculosis—Today and Tomorrow"—SIDNEY J. SHIPMAN, M.D., San Francisco

SUNDAY, DECEMBER 13, 1953

"New Drugs"—HENRY GIBBONS III, M.D., San Francisco

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Dr. Ian Macdonald, Los Angeles, chairman of the Cancer Commission of the California Medical Association, was elected president of the California division of the American Cancer Society at a meeting of the organization held recently in San Francisco. **Dr. Andrew H. Dowdy** of Los Angeles was elected secretary. Dr. Otto Pflueger, Dr. Robert A. Scarborough and Dr. David A. Wood of San Francisco and Dr. Russell Fisher and Dr. E. M. Butt of Los Angeles were elected to the executive committee of the California division.

* * *

Dr. Paul D. Foster and **Dr. R. De Barondes** of Los Angeles were awarded fellowships in the American Medical Writers' Association at the tenth annual meeting of the organization which was held in Springfield, Illinois, in September. The awards are made "in recognition of high qualifications, personal and professional, and of established standing as a medical writer, journalist or publisher."

* * *

The International College of Surgeons will hold a regional meeting of the United States Section, including the states of California, Nevada, Oregon, Arizona and Washington, at the Ambassador Hotel in Los Angeles on Saturday and Sunday, November 28 and 29, 1953.

SAN FRANCISCO

The appointment of **Dr. George B. Robson** of San Francisco as acting assistant dean of the Stanford University School of Medicine was announced recently by Wallace Sterling, president of the University. Dr. Robson will continue in private practice. At the same time, Warner P. Geigenmuller was promoted from assistant superintendent to superintendent of Stanford hospitals.

Two new appointments to the faculty of the medical school also were announced. Dr. Benton D. King was named associate clinical professor of surgery and Dr. John D. Blair assistant clinical professor of surgery.

* * *

Dr. Henry Gibbons, III, of San Francisco, was elected president of the State of California Board of Medical Examiners at a meeting of the board late last month. Dr. Gibbons has been a member of the board since February 1952. **Dr. Frank Otto** of Los Angeles was elected vice-president and **Dr. Louis Jones** of Roseville was reelected secretary.

* * *

The election of **Dr. Walter Beckh** of San Francisco to the presidency of the California Society of Internal Medicine was announced by the society last month following the annual meeting held at Yosemite National Park. Dr. Paul I. Hoagland, Jr., of Pasadena, was elected vice-president and Dr. James H. Thompson of San Francisco, secretary-treasurer.

Dr. Francis Scott Smyth, dean of the University of California School of Medicine, San Francisco, has been appointed by President Eisenhower to the Board of Foreign Scholarships for a term of three years.

The board is concerned with the management of the Fullbright Fellowship program of the Department of State.

* * *

Dr. Robert Wartenberg, clinical professor of neurology, University of California School of Medicine, has been elected an honorary member of the Association of German Neuropathologists.

SAN JOAQUIN

Dr. Freeman H. Adams on October 1 became superintendent and medical director of Stockton State Hospital, succeeding **Dr. Thomas W. Hagerty,** who retired after serving four years in that position. Dr. Adams has been on the staff of the hospital since 1946 and had served as assistant superintendent for more than a year.

GENERAL

The seventeenth annual meeting of the **New Orleans Graduate Medical Assembly** will be held March 8 to 11, with headquarters at the Municipal Auditorium. Announcement of the meeting said that 18 outstanding guest speakers will participate and that their presentations will be of interest to both specialists and general practitioners. The program will include discussions on many topics of current medical interest, in addition to clinicopathologic conferences, symposia, three dimensional surgical motion pictures, round-table luncheons and technical exhibits.

Details are available at the office of the Assembly, Room 103, 1430 Tulane Avenue, New Orleans 12, Louisiana.

* * *

The eighth annual University of Florida midwinter **seminar in ophthalmology and otolaryngology** will be held at the Sans Souci Hotel in Miami Beach the week of January 18. The lectures on ophthalmology will be presented on January 18, 19, and 20, and those on otolaryngology on January 21, 22, and 23. A midweek feature will be the midwinter convention of the Florida Society of Ophthalmology and Otolaryngology on Wednesday afternoon, January 20, to which all registrants are invited.

The seminar lecturers on ophthalmology this year are Dr. W. B. Anderson, Durham, N. C.; Dr. W. P. Beetham, Boston; Dr. W. C. Owens, Baltimore; Dr. A. B. Reese and Dr. M. C. Wheeler, both of New York City. Those lecturing on otolaryngology are Dr. E. N. Broyles, Baltimore; Dr. H. P. House, Los Angeles; Dr. W. J. McNally, Montreal, Canada; Dr. Dorothy Wolff and Dr. D. Woodman, New York City.

* * *

The annual **meeting of the American Heart Association** in 1954 will be held at the Conrad Hilton Hotel in Chicago. The Assembly Panels and the General Assembly will be held on Thursday and Friday, April 1 and 2, and will be followed by a specific scientific program on clinical cardiology on Saturday and Sunday, April 3 and 4, conducted under the auspices of the newly formed Section on Clinical Cardiology of the Scientific Council. These sessions will immediately precede the annual meeting of the American College of Physicians.

POSTGRADUATE EDUCATION NOTICES

RESEARCH STUDY CLUB OF LOS ANGELES

23rd Annual Clinical Convention of Ophthalmology and Otolaryngology

Date: January 18 through January 29, 1954. Each applicant must be a member in good standing of the American Medical Association in order to become eligible for attendance.

Fee: $100.00.

Contact: Pierre Violé, M.D., Treasurer, 1930 Wilshire Boulevard, Los Angeles 5, Calif.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES

In Los Angeles

Dermatology in General Practice (limited to 20 students).

Date: Nov. 11 to Dec. 16 (date changed from Oct. 7 to Nov. 11). Spring dates: Feb. 17 to March 24.

Fee: $30.00.

Surgical Anatomy (limited to 30 students).

Date: November 5, 1953-January 27, 1954.

Fee: $75.00.

Dermatology Conference.

Date: February 11, 12, 1954.

Fee: $35.00.

Anesthesiology.

Date: Spring, 1954.

Fee: Details to be announced.

In Long Beach:

Techniques of Hypnosis (limited to 15 students).

Date: October 9, 1953.

Fee: $100.00.

Office Gynecology.

Date: Nov. 19, 20, 21.

In West Los Angeles:

Advanced Course Techniques and Application of Hypnosis (limited to 15 students).

Date: October 23, 1953.

Fee: $100.00.

Contact: Dr. Thomas H. Sternberg, Head of Postgraduate Instruction, Medical Extension, University of California, Los Angeles 24, California.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Ophthalmological Conference. University Extension Building, 540 Powell Street, San Francisco. A four-day program on diseases of the eye, including three periods of instruction in eye surgery on animals; symposia on external diseases, muscular defects, glaucoma, cataract, neurophthalmology, therapeutics, retinal detachment. Friday evening at 8:00 p.m., the Eighth Francis L. Proctor Lecture: "Delayed Restoration of the Anterior Chamber," by Dr. Peter C. Kronfeld, Professor of Ophthalmology, University of Illinois School of Medicine.

Date: December 2, 3, 4, 5, 1953.

Fee: $75.00.

Microscopy and Photomicrography.

Date: January 14 to June 3, 1954.

Contact: Office of Medical Extension, University of California School of Medicine, University of California Medical Center, San Francisco 22, California.

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Ophthalmology Conference. Registration will be open to physicians who limit their practice to the treatment of diseases of the eye; or eye, ear, nose and throat. Registration limited to thirty physicians. Instructors will be Dr. A. Edward Maumenee, Dr. Dohrmann K. Pischel, Dr. Jerome W. Bettman, Dr. Max Fine, Dr. Earle H. McBain, and Dr. Arthur J. Jampolsky.

Contact: Office of the Dean, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15, California.

STOCKTON POSTGRADUATE STUDY CLUB

Fall Lecture Series, 1953

November 19—Treatment of Infertility, Sterility and Habitual Abortion—Abraham R. Abarbanel, M.D., College of Medical Evangelists, Los Angeles.

SEMINARS OF THE ALUMNI COMMITTEE OF THE CHILDREN'S HOSPITAL, SAN FRANCISCO

December 5, 1953—Surgery and Anesthesia in Childhood, with a discussion on the effects of hospitalization on the young child for surgical procedures.

January 23, 1954—The Problems of Prematurity and the Newborn Infant.

March 30, 1954—Acute and Chronic Infections and the Choice of Antibiotics in Treatment.

April 24, 1954—Childhood Ecology, with a discussion of physical, mental and emotional growth and development of the young child; the effects of deprivation of maternal care, and the impact of environment on the child.

A fee of $15.00 will be charged for attendance at all the seminars and those who wish to have further details or be on the mailing list for such details may write to: H. E. Thelander, M.D., Children's Hospital, 3700 California Street, San Francisco.

THE PHYSICIAN'S *Bookshelf*

YOUR CHILD AND HIS PROBLEMS—A Basic Guide for Parents. Joseph D. Teicher, M.D., Director, Child Guidance Clinic of Los Angeles, Attending Physician (Psychiatry), Children's Hospital, Los Angeles; formerly Psychiatrist in Charge, Child Guidance Clinic, St. Luke's Hospital, New York City. Little, Brown and Company, Boston, Mass., 1953. 301 pages, $3.75.

Of the many books now coming out for the guidance of parents concerning the management of their children, this is one which the physician can recommend as psychiatrically sound and based upon extensive clinical experience. While the book, purportedly, is directed primarily to parents, the physician may find its clinical orientation and its wealth of suggestions useful in his opportunities to counsel parents in regard to the normal development of children, their management, and the common difficulties met in their socialization.

The book is simply and interestingly written, and the chapters are well outlined with topic headings. It begins with a consideration of parental feelings before and after the birth of a child, describes the normal personality development of the infant, and advises in regard to management of the child's eating, toilet and sleeping routines. Chapters are then devoted to such topics as sexual education, jealousy, fears, play and possessions, and "limitations, frustrations, and doing the right thing." "Family stress and strains" are also discussed with an understanding of, and sympathy for, parental difficulties. The contents also include chapters on children's school problems, the effect of comic books, radio, movies, and television upon children, and the psychological handling of physical illness and handicaps. There is even an attempt to explain to parents the use of psychological tests.

To the extent that parents are mature, reasonably well adjusted themselves, and thus capable of making use of information and advice, this book should well serve in the interests of the mental health of children. Parents who are disturbed by their own emotional and social difficulties, however, and those whose faulty relationship to their children is determined by inner forces of which they are unaware, will be able to make the best use of the knowledge contained in this book only if it comes to them through a therapeutic relationship with their physician.

* * *

THE CONCEPTION OF DISEASE—Its History, Its Version and Its Nature. Walther Riese, M.D., Philosophical Library, New York, 1953. 120 pages, $3.75.

Meditation is a gentle art, reputedly best practiced in a quiet place—by mountain stream, by lake, on distant peak—but in the noise-rent city or gusty seashore it seems to lead to introspection. And this in turn, if pen and paper be nearby, to treatise philosophic or book conceptual.

This small book skims through the author's conceptions of the Stoic, Platonic and anthropologic viewpoints of disease, pauses to consider the moral and artistic aspects, and then plunges into a series of short chapters on the Hippocratic, Baglivian, Galenic and anatomic conceptions. Then follow sections on the social, psychologic, ontologic and, believe it or not, biographic conceptions. Finally, after a short excursion through the dialectic underbrush, the metaphysical conception is reached.

Some of the passages are refreshing and highly informative, but many seem to this reviewer to bear the ponderous glove. We are reminded that Plato held that disease was the result of excess or defect of the four corporal constituents (earth, fire, water and air). Proper proportions of these were held to be equally essential for health. Conversely, the relations of soul and body should be in equal balance. A relatively large or impassioned soul convulsed the inner man; too large or strong a body debased the soul. . . . "ignorance being considered the greatest of diseases." A verity indeed.

The chapter on disease and art travels the well-worn ground of impressionistic and expressionistic art forms, debating the difficulty of distinguishing the psychotic from the unconventional, and stressing that while disease may stimulate talent it does not create art. Freud bears not infrequent reference, and Nietzsche a modicum.

The author's own conception of disease is suggested by his emphasis that disease and the individual are both abstractions, ergo all is abstract and nature escapes our knowledge. Perhaps it should have been added that disease is a commonality and therefore a relatively normal phenomenon, just as discord, unhappiness and war are normal, whereas health, tranquillity and peace are distinctly rare, or unusual, or in other words abnormal.

The gentle and confused reader may now wish to return to Thomas Sydenham who observed "A disease, in my opinion, how prejudicial soever its causes may be to the body, is no more than a vigorous effort of nature to throw off the morbific matter, and thus recover the patient."

* * *

CHILD DEVELOPMENT—The Process of Growing Up in Society. William E. Martin and Celia Burns Stendler, Professor of Education, University of Illinois—under the editorship of Willard B. Spalding, Oregon State System of Higher Education. Harcourt, Brace and Company, New York, 1953. 519 pages, $6.50.

This is a textbook in child development. Accordingly, it is organized for a systematic study of the subject, contains throughout provocative questions for discussion, includes 32 pages of photographic illustrations (also a sprinkling of cartoons), and concludes each chapter with a small but well selected and recent bibliography for further reading. It is more than a description of child behavior at the various stages of development with which physicians are becoming more or less familiar; rather, it draws upon the fields of biology, physiology, pediatrics, sociology, anthropology, and

psychology in an attempt to explain how children become socialized.

The book is divided into four parts. Part I discusses the child as a human being. It begins with a consideration of the child's biological inheritance, proceeds to a study of the principles of growth and development and the basic motivating forces, points out the significance of individual differences, and concludes with a description of development in infancy. Part II is concerned with the meaning of society and culture and their effect upon the development of personality, and Part III is devoted to the process of socialization. In Part III, there is a description of the American character from the anthropological point of view, and also contrasting descriptions of the psychoanalytic and "sociopsychologic" points of view in regard to personality and character development. Part IV takes up the family, the school, the peer groups, and the community (including the church and media of mass communication) as socializing agencies.

It is the reviewer's opinion that this work may well serve several groups as an introduction to the study of child development. It should prove valuable as a basic text for parent and teacher study groups. It should have a place on the reading list of students in elementary psychology, nurses, and pediatric resident staffs. The physician will find some of the biological discussions quite elementary, but a perusal of the book may help him to place his knowledge in proper perspective from the viewpoint of the child as a developing social being. It will provide him with useful concepts from other fields rather than with advice as to the management of behavior problems.

* * *

MULTIPLE MYELOMA. I. Snapper, M.D., Director of Medical Education, Cook County Hospital; Louis B. Turner, M.D., Research Assistant in Medicine, Mount Sinai Hospital, New York; and Howard L. Moscovitz, M.D., resident, Second Medical Service, Mount Sinai Hospital, New York. Grune & Stratton, New York, 1953. 168 pages, $6.75.

This fine monograph by Dr. Snapper and his associates is likely to be the standard reference work on multiple myeloma for many years to come. Although the subject is covered in a systematic and scholarly manner, the style is such that the material is interesting and readable. The book is primarily aimed at clinicians, and its subject matter is based largely upon almost one hundred patients treated by the authors. Illustrative case histories from these patients, as well as radiological, pathological, and metabolic data are frequently used to supplement the text. This happy combination of description and illustration conveys to the reader a first-hand familiarity with the subject not often found in medical texts.

Although the emphasis is primarily clinical, the metabolic aspects of multiple myeloma are not neglected. The sections on the renal lesion of myeloma, and effects on protein metabolism are especially noteworthy. Bence-Jones protein is discussed in some detail, and accurate methods for its identification are described. Together with an account of serum electrophoretic changes are simple clinical methods to demonstrate hyperglobulinemia.

The chapter on therapy reflects the current inadequacy of all available agents in the treatment of multiple myeloma. In the discussion of stilbamidine there is seen, perhaps, a wistful nostalgia for a drug introduced by the senior author. This is accompanied by a frank admission of its shortcomings, so that no harm is done.

The growing trend toward detailed monographs on a single disease is thoroughly justified if the calibre of this volume can be maintained.

THERAPEUTICS IN INTERNAL MEDICINE—2nd Edition. By 84 authors; edited by Franklin A. Kyser, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School. Hoeber-Harper Book, Paul B. Hoeber, Inc., 49 East 33rd Street, New York 16, 1953. 85. pages, $15.00.

This is a good conventional reference book for therapeutics in internal medicine. It follows the routine outline of chapter presentation. It gives comparatively little space to general subjects. While it lacks any spectacular or unusual approach to lift it from the general run of books on therapy, it is written carefully and covers well the broad field of internal medicine.

The book could offer more variety in therapy, and if one is confronted with a difficult problem, it may prove inadequate. For example, take a woman with exfoliative dermatitis, whose disease is complicated by an advancing hepatorenal syndrome: contact dermatitis is mentioned but given short shrift as a skin disease; lower nephron nephrosis likewise is mentioned but the write-up is not helpful; nor are the two conditions correlated in any place.

Some of the sections, for instance those on the heart and hypertension (which are generally good) should give more exact dosage and specific preparations: on pages 476 and 477 the dosage of a mercurial diuretic is noted as 0.5 to 1 cc. intramuscularly daily, after which "the patient is then put on a maintenance dose which may be given every 1-2 weeks as indicated." There is such a variety of mercurial diuretics available that this advice becomes irresponsible and the author may as well counsel the reader to consult his local pharmacist or manufacturer's sales representative. It seems a better idea to give names and dosages of specific preparations with the trade names in parenthesis—as they are given elsewhere in the book.

Despite these defects, the solid character of this volume recommends it highly for the reference desk of the internist and other students of medical diseases.

* * *

PHYSICAL DIAGNOSIS. Harry Walker, M.D., F.A.C.P., Professor of Clinical Medicine, Medical College of Virginia, Richmond, Virginia. The C. V. Mosby Company, St. Louis, 1952. 461 pages, 126 illustrations, $8.00.

This is a volume of modest size produced under the joint authorship of several members of the Medical College of Virginia. It is divided into two sections, the first and larger of which deals with general physical examination. The second section is devoted to specific diseases of the respiratory and circulatory systems. The illustrations, although too few, are of good quality.

There is considerable variation in the quality of different contributions. While there is an excellent chapter on "Physical Diagnosis of the Female Pelvic Disease," the section on the abdomen is rather spotty. Apparently in an effort to conserve space, one finds summary statements such as the following (pages 191-192): "Liver enlargement occurs in fatty infiltration of the organ, chronic passive congestion, cystic disease and cirrhosis."..."A tender liver, manifested by pain on pressure, occurs in acute passive congestion, hepatic abscess and perihepatitis." There is no mention here of acute hepatitis, a condition considerably more common and therefore of greater import to the student beginning physical diagnosis. The fluid wave is described as a physical sign but there is no statement that it is more significant in the erect or sitting position.

The prime value of this book will be in the teaching of physical diagnosis to the second year students, and it will naturally find its greatest application at the Medical College of Virginia. Since it is incomplete and does not make an outstanding contribution, it is doubtful that California medical schools will substitute it for the texts now in use.